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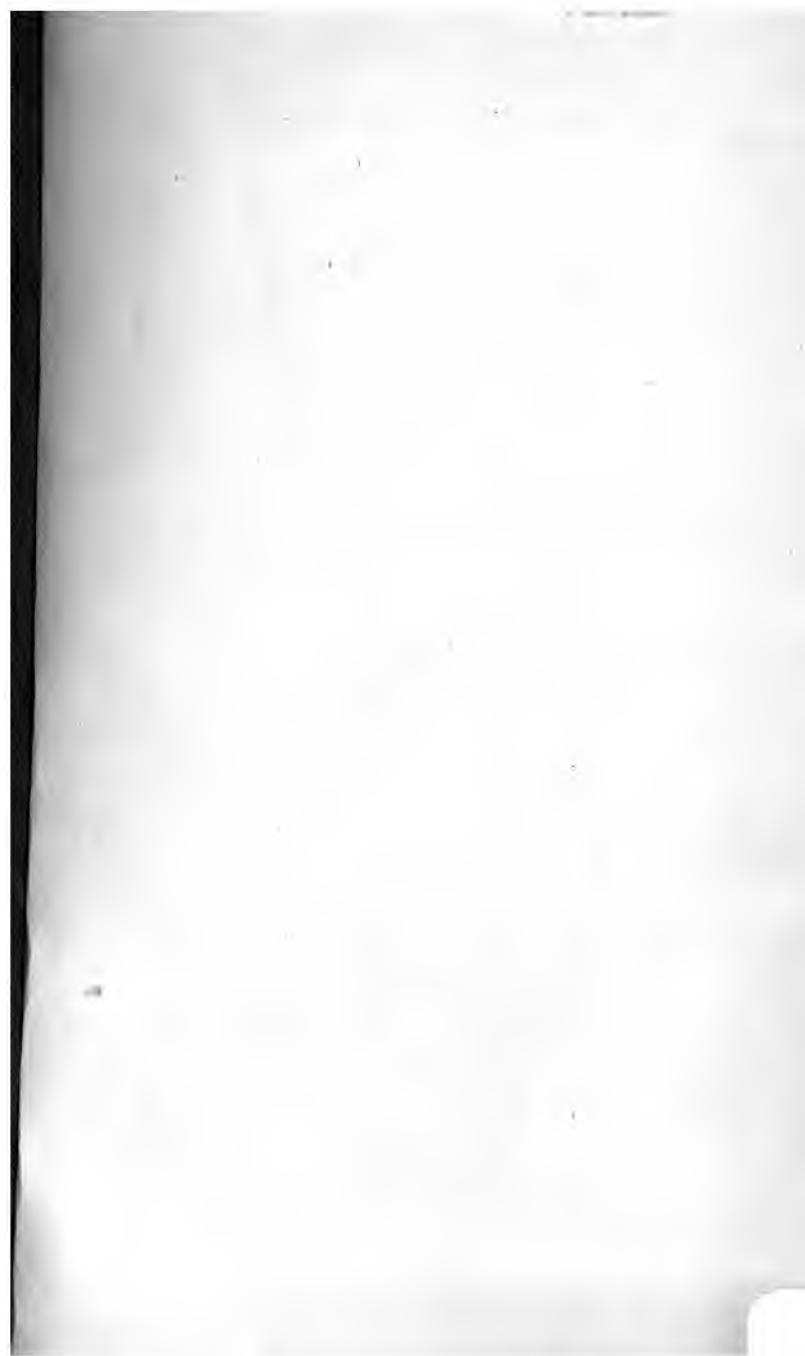


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The Pharmacology of Useful Drugs

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PREFACE

This book is a reprint, with numerous additions, of the matter presented in *The Journal of the American Medical Association* under the heading "Practical Pharmacology." It is an attempt to present, in simple language, the pharmacology of those drugs with which the practitioner is mostly concerned. The new advances in pharmacology are stated and their practical application to the treatment of disease is indicated. Under each subject are given the pharmacology, therapeutics, dosage, and materia medica of the drugs discussed. For the convenience of the practitioner it has been issued in a handy pocket size. It is hoped that this work will prove of service to those who practice modern scientific medicine.

42263

Abbreviations

The following abbreviations occur in the text:

U. S. P.—The Pharmacopeia of the United States of America, Eighth Revision.

N. F.—The National Formulary of Unofficial Preparations, Third Edition.

N. N. R.—New and Nonofficial Remedies, 1913.

w/v—The relation of the weight of active constituents to the volume of liquid preparations.

Statement of Solubility

For ease of reference, the solubility of official articles is indicated in approximate terms in accordance with the following equivalents:

Substances that are soluble in:

Less than 1 part of solvent = very soluble.

From 1 to 10 parts of solvent = freely soluble.

From 10 to 100 parts of solvent = soluble.

From 100 to 1,000 parts of solvent = slightly soluble.

From 1,000 to 10,000 parts of solvent = very slightly soluble.

From 10,000 to 100,000 parts of solvent = nearly insoluble.

More than 100,000 parts of solvent = practically insoluble.

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THE PHARMACOLOGY OF USEFUL DRUGS

INTRODUCTORY

The greater part of the material comprising the present volume was published in a series of articles in *The Journal of the American Medical Association*. In the following pages we will discuss the pharmacology,¹ the chief therapeutic uses and the materia medica of those drugs which have been accepted by the Council on Pharmacy and Chemistry for inclusion in the "Handbook of Useful Drugs."²

Several years ago *The Journal* published a somewhat similar volume under the title "The Pharmacopeia and the Physician," and while the same general plan will be followed in the present volume, the discussions will be limited almost entirely to the really essential drugs of the materia medica, as indicated in the title.

It is evident that the therapeutic use of drugs requires some knowledge of their pharmacologic actions, but many physicians fail to appreciate the true value of pharmacology. Frequently, too, it is impossible to distinguish the literature of the disinterested investigator from that issued by those who are commercially interested in the products which they discuss.

We trust that the present treatment of the subject, so far from satisfying the reader, may stimulate him to further inquiry and the perusal of the larger works on pharmacology and therapeutics.

1. The terms "materia medica" and "pharmacology" are often used somewhat loosely. *Materia medica* treats of the physical and chemical properties of drugs and of their pharmaceutical preparations. Pharmacology, or pharmacodynamics, treats of the actions which drugs exert on normal animal tissues or organs. For example, the paralysis of vagus endings in the heart by atropin is one of its pharmacologic actions.

2. The Council has made a careful selection of all drugs and preparations, irrespective of their nature, whether official or unofficial, proprietary or non-proprietary, which seem to be the best for the treatment of diseases, and these have been included in the little volume entitled, "A Handbook of Useful Drugs."

The pharmacology of the different drugs will be discussed very briefly in some cases, somewhat more comprehensively in others, but sufficiently in each case to afford a basis for the best therapeutic use of the drug under consideration. The discussion of quinin and digitalis, respectively, illustrates the principle followed. Quinin finds its greatest use in the treatment of malaria, in which its value depends on its killing the organisms which are found in the blood, and the secret of the successful employment of quinin is to get the requisite amount in the blood at the proper time; hence dosage and methods of administration are of greater importance in that case than a knowledge of the various other pharmacologic actions of quinin, beyond the mere fact that it is a general protoplasm poison, and consequently injurious to all tissues with which it comes in contact in sufficient concentration. Digitalis, on the other hand, does more harm than good in the hands of those who use it without a pretty accurate knowledge of its pharmacologic actions; it becomes necessary, therefore, to devote more attention to the pharmacology of digitalis than to that of quinin.

Drugs produce their effects by increasing or decreasing the normal functions of the structures on which they act, and in so doing they do not themselves produce an appreciable amount of energy. The failure of a drug to produce its expected therapeutic effects may often be explained by the condition of the organ on which it acts. A grasp of this relationship between drugs and the organism will serve to simplify the understanding of their uses and limitations, and will often prevent disappointment.

Every drug exerts a variety of actions, but only a few of the actions of any drug are of benefit in any given condition; the others are negligible or detrimental. Thus, in the treatment of night sweats, atropin is used on account of only one of its many actions, namely, its power of limiting secretion.

The therapeutic usefulness of a drug depends on the fact that it exerts a far greater action on certain organs or tissues than on others. Strychnin, for

example, is capable of combining with certain cells in the central nervous system and affecting them profoundly, while leaving the other cells of the body practically unaffected.

The influences of age, sex, weight, diet and many other factors which modify the actions of drugs are generally recognized and do not call for detailed discussion here, but every physician encounters occasional disappointment in the use of a drug on which he has come to rely, and we shall point out some of the most common causes of the variability of action, which are frequently overlooked because they are deemed of too little importance to merit careful consideration.

ABSORPTION AND ELIMINATION

The intensity of the action of a given drug usually depends largely on the total amount which acts at one time, and this is determined to some extent by the ratio between the rate of absorption on the one hand and that of elimination or destruction in the body on the other. A large dose of a drug may produce less effect at one time than a small dose administered in the same way at another time, the difference in the intensity of action being due to differences in the rates of absorption and elimination.

The degree of dilution in which a salt is administered not only influences the intensity of a given action, but may even determine its nature. A concentrated solution of magnesium sulphate may cause nausea, whereas the same amount of the salt in dilute solution will cause purgation. Magnesium sulphate usually causes only watery diarrhea when it is administered orally, but it has been known to cause death when administered in this way, because of its rapid absorption and slow elimination.

A common cause of disappointment is the want of exact knowledge concerning the absorption of drugs. It is often asserted, and accepted without question, that because a given substance is very soluble in water, it must necessarily be absorbed readily from the alimentary canal. Disregarding the relatively slow absorption of soluble purgative salts, we may call

attention to the fact that for some unknown reason, some of the very soluble glucosids are absorbed slowly and irregularly from the gastro-intestinal tract; also that certain glucosids or resins which are wholly insoluble in water are absorbed fairly rapidly from the gastro-intestinal tract. In other words, we must recognize the fact that every drug is a law unto itself in regard to its rates of absorption and elimination.

Most drugs are not absorbed readily from the stomach, but must pass into the duodenum before absorption begins; it may follow, therefore, that when the gastric movements are interfered with by disease or drugs, and especially when the pylorus remains in tonic contraction, as it does at times after large doses of morphin have been taken, drugs may remain unabsorbed in the stomach for hours after oral administration. Drugs should be administered subcutaneously or by the rectum when it is suspected that the gastric contents will be prevented from passing into the duodenum in the usual manner.

Comparatively few drugs are absorbed from the unbroken skin, and the use of ointments and plasters containing active alkaloids is irrational in the main; the good results which may follow their use in most instances are not due to the alkaloids. For example, in the case of opium and lead wash — a most unscientific mixture, since the morphin in that case is valueless — the beneficial results are due to the astringent action of the lead water. A few substances which are readily miscible with oils and fats penetrate the skin sufficiently to act on the sensory nerve-endings, but our knowledge of this subject is far from complete.

Another cause of disappointment lies in the fact that physicians sometimes forget that locally acting drugs may fail to exert an effect after absorption similar to that observed in the alimentary canal. Tannin, for example, acts as an astringent on the mucous membrane of the gastro-intestinal tract after its oral administration, but it is not absorbed in the free state and after absorption it does not exert an astringent action. Antiseptics are sometimes recommended for their action on micro-organisms in the

circulating blood, but such misleading advice occurs chiefly in the literature distributed by the exploiters of nostrums.

We are not so well informed as we should be even on the subject of dosage; it is often stated as a rule that the oral dose of a given drug is about twice as large as the subcutaneous dose, and that the rectal is about twice the oral. These ratios apply to very few drugs indeed; the attempt to regulate the dosage of some drugs by this rule would result disastrously. In fact, death has resulted from the subcutaneous injection of an amount of strophanthin equal to one-half of the oral dose. This illustrates the necessity for a better acquaintance with a few drugs, rather than a superficial knowledge of a large number. At best drugs are like two-edged swords capable of doing harm if used improperly, and if we assume the responsibility of using them we owe it to our patients to know as much as possible about their actions.

SYNERGISTIC ACTIONS

It was formerly customary to use mixtures of many drugs having supposedly related actions without any clear idea of their synergistic effects, but such mixtures are not used at present by educated physicians, for we are coming to have a better understanding of the synergistic actions of drugs which are useful in some cases and harmful in others. Some of these synergistic actions will be discussed when we consider the drugs exhibiting them.

MODES OF ADMINISTRATION

Drugs should be administered by the mouth except in those cases in which the oral method is contraindicated. While the other methods advocated from time to time may be suitable for special cases, and in the hands of those who have developed a special technic, the oral administration will suffice in the vast majority of cases.

The intravenous injection of a variety of drugs has been advised, but this method is distinctly dangerous

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in the hands of any one who is not skilled in its use, and it is often disappointing even with the best technic.

Compressed tablets of insoluble drugs do not always disintegrate rapidly in the stomach, and such drugs are preferably given in the form of mixtures or as dry powders, which may be enclosed in capsules. Many of the ready-made pills tend to become harder and less readily disintegrated when long kept. Freely soluble salts, such as potassium bromid, taken in doses of 0.3 gm. (5 grains) or more, may give rise to gastric irritation with nausea, when they are administered in concentrated solution, or in the form of compressed tablets, which form concentrated solutions on dissolving in the stomach. Such salts should be dissolved in about thirty times their weight of fluid before being administered.

Nausea and vomiting sometimes follow the administration of various drugs. When this symptom arises from local irritation of the stomach it may be avoided either by dilution or by a different mode of administration. In other cases, as in members of the digitalis group, the nausea and vomiting, being due to a stimulation of the vomiting center in the medulla, are not influenced by the mode of administration. In such cases, nausea is to be avoided only by regulation of the dose. Before resorting to inconvenient methods of administration, therefore, one should be certain that the method proposed will actually give relief from the disagreeable symptom.

Idiosyncrasy, tolerance and cumulation, so called, will be discussed in connection with those drugs in the use of which they are important factors.

MULTIPLICATION OF PREPARATIONS

The present era of pharmacy and therapeutics is marked by the multiplicity of alleged remedies urged on the attention of the prescriber. This multiplication of preparations is attributable largely to the influence of commercial interests, which have often had more weight than considerations of pharmacologic and medical science and have overshadowed the interests of the sick.

In this confusion physicians will often find themselves at a loss how to choose wisely the most efficient agent. A careful study of the new remedies offered will show that few present any new therapeutic action or are specifics for particular diseases. Most of those which are worthy of consideration claim advantage over the older remedies in the avoidance of disagreeable side effects. In a considerable number of cases these claims have not been realized, and the preparations are nothing but encumbrances to our *materia medica*. Before accepting a manufacturer's claim that his preparation is preferable because it avoids undesirable by-effects, one should make sure that this freedom from disagreeable effects is not accomplished by lack of therapeutic efficiency.

In choosing therapeutic agents, the practitioner will gladly welcome the help extended by the Council on Pharmacy and Chemistry in sifting the mass of evidence presented and commending for use the remedies listed in the new volume, "Useful Drugs." In admitting preparations to the book *New and Nonofficial Remedies*, the Council has adopted a liberal policy; it has admitted any drug which has probable value if exploited in an unobjectionable manner. Though the Council has been in existence for more than ten years and though during that time manufacturers have been afforded ample opportunities for submitting evidence of any advantages which their preparations possess, among the thousands of these advertised to physicians, only about 250 are enumerated in *New and Nonofficial Remedies*, and of this number not more than a score have been found of sufficient importance to merit inclusion in the "Handbook of Useful Drugs," for admission to which evidence of merit is essential.

It is obviously impossible to discuss any considerable number of popular nostrums in this volume. A few of them, however, will be mentioned, chiefly to show the methods of misrepresentation employed in their exploitation, and the necessity of fostering the use of standard drugs of proved value and well-known side actions for which proper allowance may be made in the administration.

These side actions deserve more attention than they usually receive. We have been prone to consider unfavorable symptoms in patients as unavoidable manifestations of the diseases from which they suffer in many cases in which the drugs were contributing causes at least. We must face the question squarely and recognize the fact that there is no such thing as an ideal drug. When a manufacturer asserts that his preparation possesses all the advantages of a given drug with none of its disadvantages, his excessive optimism is obvious.

CLASSIFICATIONS OF DRUGS

Buchheim classified drugs about sixty years ago according to their more prominent pharmacologic actions, and this classification has been retained with some modifications to the present time, despite the fact that it has many disadvantages. No strict classification is possible, because every drug has a variety of actions, and no two have exactly the same range of activities.

We shall make no effort to classify the drugs in any rigid way in the following pages, and it is understood that any grouping attempted is merely suggestive and intended to facilitate the convenient discussion of the various drugs.

CHAPTER I.—DRUGS WHICH ACT ON THE CENTRAL NERVOUS SYSTEM

We may consider the drugs of these groups with reference to the dominant action, whether it be stimulation or depression, and with reference to the part of the nervous system on which they exert the most pronounced effect. The action of a drug is never limited to one part of the central nervous system; though in a given case it may be exerted mainly on the brain, medulla or cord. Few drugs produce stimulation without some subsequent depression, or depression without at least fleeting stimulation.

Drugs which act mainly on the central nervous system will be classified as follows:

A. Stimulants: 1. Drugs acting mainly on the spinal cord, but having important actions on the medulla (strychnin group).

2. Drugs acting mainly on the medulla, but having important actions on the brain or cord (atropin group).

3. Drugs acting mainly on the brain, but with important actions on the medulla or cord (caffein and theobromin).

B. Depressants: 1. Drugs which act on the brain first, then on the medulla (morphin group).

2. Drugs which act mainly on the heat and pain centers (antipyretics and analgesics).

3. Drugs which depress first the great brain, then the cord and the medulla last (hydrocarbon narcotics). (Order of involvement of first importance.)

This classification (like others used in this volume) is only approximate, and no attempt will be made to adhere to it rigidly.

A. STIMULANTS

STRYCHNIN

There are several drugs which act on the spinal cord much as strychnin acts. While this is of some importance as a side action, strychnin and nux vomica are virtually the only drugs which are used therapeutically for increasing the reflex activity of the cord.

Thebain (an alkaloid occurring in opium) has an almost pure strychnin-like action on the cord, and caffein, morphin and codein possess the action to some extent, though they rarely exhibit it in man. Caffein and codein are seldom given in doses large enough to cause any increased reflex excitability. In morphin poisoning in man death results from paralysis of the respiratory and other centers before the action on the cord has time to develop. In view of the subsidiary importance of reflex stimulation in the action of those drugs, the present article deals almost entirely with strychnin.

Strychnin¹ acts on the spinal cord of vertebrates in such a way that the reflexes are increased, the effect increasing with the size of the dose, so that with the largest therapeutic doses in man there is distinct twitching of the voluntary muscles, and with larger doses any slight stimulus, such as touching, induces a convulsive movement involving the closely related groups of muscles. If an excessive dose has been given, a stimulus which induces any reflex movement at all suffices to cause a convulsion involving all the voluntary muscles of the body. The intensity and duration of the convulsions increase with the size of the dose. The convulsion is followed by a period of

1. In practically all cases, the actions of alkaloids are so nearly like those of their salts that they are discussed together. It is understood that the salts contain a small amount of acid, which is negligible so far as the pharmacologic actions of the alkaloids are concerned, but for which allowance must sometimes be made in calculating the dose. The principal reason for using salts of the alkaloids is that the salts are more soluble than the alkaloids themselves.

depression varying from a few seconds to some minutes, and usually becoming longer with successive convulsions; but death may follow the first convulsion.

Strychnin convulsions are typical; there is at first a sudden contraction of the voluntary muscles, and if the dose has been very large this is immediately followed by tetanus with opisthotonos, the convulsion terminating with a few clonic jerks, followed by the pause during which the reflexes are actually depressed. If the first convulsion was brief, the depression may be followed almost immediately by a second convulsion if any stimulus is applied, or after an interval the length of which depends on various circumstances. The succeeding convulsions are almost exactly like the first in character, but they may be of shorter or longer duration.

ACTIONS OF STRYCHNIN ON THE MEDULLA

The actions of strychnin on the respiratory and vasomotor centers in the medulla probably differ only in degree from those on the cord, but it is difficult to determine the precise nature of this action on the medullary centers, and opinions differ as to the value of strychnin in conditions of circulatory depression.

When a normal animal is anesthetized and strychnin is injected into the circulation, no appreciable effect on the blood-pressure is produced until an amount is given equal to that which causes a distinct increase in the reflexes in a normal animal. Touching or pinching then causes a sudden rise of blood-pressure and a rapid return to normal. If a convulsive dose is injected, the rise in blood-pressure corresponds in duration to the convulsion. This rise of blood-pressure is wholly independent of any spasm of the voluntary muscles, for it occurs in exactly the same way in curarized (motionless) animals.

It is impossible to state whether or not therapeutic doses of strychnin affect the vasomotor centers so as to increase the blood-pressure when this is abnormally low, but it seems probable that in pathologic conditions with low blood-pressure, strychnin may render the vasomotor centers more susceptible to stimulation, and it is certain that it affects the circula-

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tion indirectly by increasing the tone of voluntary muscles through its action on the spinal cord in suitable cases.

The action of strychnin on the respiratory center is probably analogous to that on the cord, rendering it more responsive to stimuli, which normally play such an important rôle in the rate and depth of respiration, and under the influence of therapeutic doses of strychnin the carbon dioxide of the blood causes an increased respiratory movement, this being more pronounced when the respiratory center has been previously depressed by a narcotic.

With excessive (convulsive) doses of strychnin the respiratory center is first stimulated and later depressed. During the convulsions the respiration ceases, owing to the rigidity of the muscles of the chest; this causes an extraordinarily rapid increase in the carbon dioxide in the blood, which stimulates the respiratory center. Nevertheless, there is an interval, following the cessation of the convulsion and before the reinstatement of respiration, during which the center is evidently depressed, but this depression is much briefer than is the depression of the cord, as a rule, and the respiration begins shortly and is then deeper or more rapid than before the convulsion.

Following large doses the respiration fails to be reinstated after one of the convulsions, it may be the first, but usually after the second or third. Though opinions differ concerning the value of strychnin as a stimulant to the vasomotor centers, there is little doubt about its being an active stimulant for the respiratory center.

Strychnin stimulates the vagus center in the medulla, causing some slowing of the heart, but the rate of the heart depends on so many factors that this effect is not pronounced with therapeutic doses.

ACTIONS OF STRYCHNIN ON THE BRAIN

Strychnin increases the reflexes in the brain, especially those of the special senses, so that vision, smell, hearing, touch and taste are rendered more acute. The effects on the eye and ear are utilized therapeutically. Strychnin sometimes exerts a marked psychic

effect, causing a feeling of exaltation and relief from fatigue. This action is quite variable, and it is impossible to state when it may be expected.

ABSORPTION AND EXCRETION OF STRYCHNIN

Strychnin exerts a much greater action when administered intravenously than when administered in any other way, but it may be absorbed fairly rapidly from the gastro-intestinal tract and exert as great an effect after oral administration as after subcutaneous injection. The full effects of the oral dose are seen usually in about half an hour; the effects of poisonous intravenous doses are exhibited almost immediately. An extract of *nux vomica*, or a pill containing strychnin and some colloidal substance, is commonly employed when slow absorption is desired with prolonged action on the local nervous mechanism in the walls of the intestine.

Strychnin probably leaves the blood-stream very rapidly, and the larger part of a therapeutic dose is almost certainly eliminated from the body within a few hours, for fairly large doses may be administered several times daily for many days without causing toxic symptoms. Cushny states that elimination is not complete for a period varying from two to eight days. Strychnin appears in the urine soon after its absorption into the blood, and an amount equal to several times the normally fatal dose has been recovered from the urine of a dog in a period of five hours, during which large amounts of solution of sodium sulphate were injected intravenously in order to induce copious diuresis. (Unpublished experiments of R. A. Hatcher.)

TOXICOLOGY

Strychnin is among the most poisonous of the commonly used alkaloids, and as little as 0.03 gm. ($\frac{1}{2}$ grain) has proved fatal to a man. It is probable that the average fatal dose for a previously healthy adult is about 0.10 gm. ($1\frac{1}{2}$ grains). With appropriate treatment patients have survived much larger doses. One should never abandon hope of saving life until it is extinct, whatever the dose taken.

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Death in strychnin poisoning usually results from respiratory paralysis, but a previously weakened heart may stop as the result of the sudden excessive rise in blood-pressure.

The method to be followed in the treatment of strychnin poisoning will depend on a number of factors, including the following: The total amount of the poison taken; the amount which remains unabsorbed (in case of its oral administration); the presence or absence of hyperexcitability or convulsions. Hence the following remarks are only intended by way of suggestion, and the treatment must always be adapted to the needs of the case in hand.

The physician will rarely be called on to treat strychnin poisoning after the administration of the drug in any way except by the mouth, because death usually follows so swiftly after the subcutaneous injection of a massive dose that no opportunity is afforded for effective interference.

So promptly does death usually follow the absorption of a fatal dose of strychnin into the circulation, that the mere fact that the patient is alive affords proof that at most but little more than the normally fatal dose has been absorbed, and when there is reason to suppose that any poison remains in the stomach, the chief efforts should be directed toward its removal or destruction.

If there is no increased reflex excitability, one should proceed to empty the stomach as quickly as possible. It may be washed with water to which strong tea² or half a pint or more of a 1 per cent. solution of potassium permanganate has been added, or with water alone if the tea or potassium permanganate is not readily available.

If the means for washing the stomach are lacking, an intramuscular injection of 6 mg. ($\frac{1}{10}$ grain) of

2. While the tannin of tea is useful as a precipitant of strychnin (Sollmann), it should be remembered that the beverage varies enormously in its tannin content. Some teas contain little tannin, and are practically useless for preparing an alkaloidal precipitant. While the physician is preparing to wash the stomach of the patient, he may have tea prepared as follows: Hot water is poured on the leaves and allowed to stand about one minute; this infusion is thrown away, because it contains caffeine, which is synergistic with strychnin, but little of the tannin. Boiling water is then poured on the leaves and allowed to stand about five minutes. This infusion contains most of the tannin and little caffeine.

apomorphin may be given at once, and strong tea or a pint of 0.5 per cent. solution of potassium permanganate may be swallowed by the patient. Should it become necessary to abolish vomiting, this may be done by inducing anesthesia with chloroform and maintaining it with ether.

If hyperexcitability has been induced while there is reason to believe that the stomach still contains a notable amount of strychnin, the treatment is not so simple. It is imperative to remove or destroy any of the poison which remains in the stomach when it is practically certain that its absorption would prove fatal despite any treatment, but the washing of the stomach or emesis would be dangerous at a time when such measures are liable to cause convulsions. Emesis is then contra-indicated, and anesthesia must be induced before the stomach-tube is passed.

An especially difficult question arises when it is known that much more than the average fatal dose of strychnin has been swallowed, and when, owing to the length of time which has elapsed since it was taken, and the severity of the symptoms present, it seems probable that much of the poison has passed into the duodenum. In such a case the poison cannot be removed by gastric lavage, and it probably cannot be precipitated or destroyed by chemical agents, yet its complete absorption must almost inevitably prove fatal.

The procedure, however, in such cases must be much the same as in those in which some of the drug is supposed to remain in the stomach, and in addition, it is necessary to empty the bowel as quickly as possible, preferably by means of a copious saline cathartic.

The measures so far discussed are concerned with the prevention of the absorption of strychnin; apart from this are the questions of antagonizing its action after absorption and of hastening its elimination, both of which enter into consideration after absorption occurs, whatever the channel of administration.

Strychnin is eliminated by the kidneys, and whatever physiologic antidote is employed it should not interfere with diuresis, which should be promoted to the utmost. Hot tea or other hot liquids will induce

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diuresis, but the action is somewhat slow, and unnecessary loss of time should be avoided; hence a large amount of hot fluid should be introduced into the stomach, while as much should be introduced into the rectum and lower bowel as can be retained with comfort. In urgent cases it would seem to be justifiable to inject a quart or more of a sterile 2 per cent. solution of sodium sulphate into the veins, under suitable precautions, of course.

The value of ether in strychnin poisoning is shown by the fact that an animal under its influence — it must be anesthetized completely — will survive an amount of strychnin equal to more than twice the fatal dose for a normal animal. Chloroform may be used to hasten the induction of anesthesia, but this should be continued with ether so long as may be necessary. Special stress is placed on the use of ether, for while hydrated chloral is commonly advised as an antidote to strychnin, pharmacologic experiments show that hypnotic doses of it are nearly, or quite, useless, and narcotic doses are dangerous in various ways. The dosage cannot be regulated so as to produce only the desired action; it is injurious to the heart; it lowers blood-pressure to the point that the respiratory center must suffer, while the elimination of the poison is seriously hindered.

Anesthesia may be maintained with ether without any of these disadvantages.

Artificial respiration should be employed when severe convulsions indicate that the respiratory center will suffer depression. One should not wait until actual respiratory failure occurs before instituting this measure. Unless the dose has been excessive, the convulsions can be controlled by this means. The inhalation of oxygen is an aid in hastening the destruction of strychnin. The treatment of strychnin poisoning may be summarized then as follows: removal of the drug from the stomach; precipitation by tannin; destruction by potassium permanganate; control of convulsions by ether; artificial respiration; elimination by copious diuresis, and avoidance of all stimuli, including touching the patient, noise and

flashes of light. The chief reliance must be placed in efforts to prevent the absorption of large amounts into the circulation, if the patient is seen in time.

THERAPEUTIC USES

Strychnin is probably not directly curative in any disease, but its capacity for increasing the activity of the reflex centers in the cord, medulla and brain suggest its employment in various conditions in which these centers are depressed, and its action on the vasomotor and respiratory centers indicates its use in various conditions attended with lowered blood-pressure and interference with respiration.

It is used in many forms of incomplete motor paralysis, but it should not be used when the paralysis results from a lesion in the cord, or in the presence of inflammation of the nerve centers; it is especially contra-indicated in the inflammatory stage of infantile paralysis (anterior poliomyelitis). Opinions differ concerning its value after the paralysis has developed. In motor paralysis due to lesions in the brain, it is useful, in moderate doses, to maintain the tone of voluntary muscles through the increased reflexes.

Respiratory stimulants are useful when the center is depressed by narcotics, including alcohol, chloroform, ether, hydrated chloral and morphin, and in diseases of the respiratory passages and the lungs, including bronchitis and pneumonia, when there is a tendency toward respiratory depression. Strychnin can be used, but it must be remembered that large doses of strychnin depress the respiratory center, after first stimulating it. Such large doses are therefore contra-indicated, especially in narcotic poisoning, in which the stimulant action of the strychnin might be entirely masked by the narcotic, and yet the late depression due to strychnin would be added to that of the narcotic. Caffein would seem to deserve the preference as a respiratory stimulant in narcotic poisoning at least.

Strychnin is often used for increasing the blood-pressure, despite the fact that no essential increase follows the administration of non-toxic doses to normal animals or men. It is quite possible that its

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effects in pathologic conditions attended with abnormally low blood-pressure may be beneficial, and, indeed, Osborne states that it is the sheet-anchor when all of the vital centers are depressed in pneumonia.

It is often used in shock, but opinions vary concerning its value in that condition. The mechanism of shock is so little understood that it is impossible to state positively what the effects of strychnin are likely to be. Crile believes that it has no value in that condition, but that, on the contrary, it is decidedly harmful, actually increasing the danger. In cases in which respiratory depression is the primary cause of shock, it seems probable that strychnin may be of value, but we have no satisfactory evidence that therapeutic doses are capable of increasing the blood-pressure directly to any notable degree in shock.

Strychnin is often used with occasional benefit in disturbances of vision (amblyopia, amaurosis) when there is no anatomic change or only incipient optic atrophy, and in impairment of hearing of central origin. It is often used to improve the tone of the weakened sphincters (in enuresis), but when there is spasm of the vesical sphincter it is contra-indicated; atropin should be used instead.

The use of strychnin as a simple bitter for improving the appetite and digestion and as an addition to cathartics will be discussed in connection with other drugs belonging to those groups.

It is often used more or less empirically in many different conditions, in some of which it is certainly useful, but in others probably useless.

It is often recommended as a "cardiac tonic," but we have no evidence of its direct action on the heart. It may slow the heart through vagus stimulation at times; it may improve the circulation through its actions on the vasomotor and respiratory centers—for one cannot wholly separate the influence of the respiration and circulation—and thus through the circulatory changes it may improve the nutrition of the heart, much as it causes improvement in the voluntary muscles and other tissues of the body, when

it improves the circulation by increasing the muscular activity.

Cecil Wall states that *nux vomica* has been termed the best hypnotic in the treatment of chronic bronchitis.

DOSAGE

The average single dose of strychnin, sulphate or nitrate, for oral administration is 0.001 gm. ($\frac{1}{60}$ grain), but the dose varies so widely that the statement of the average dose does not convey much information unless the purpose for which it is to be used is indicated. As little as 0.00065 gm. ($\frac{1}{100}$ grain) is often used as a bitter tonic, and as much as 0.010 gm. ($\frac{1}{6}$ grain) may be given daily for short periods. Much larger doses have been used, but there is no satisfactory evidence that they are necessary, and their use is attended with danger. The dose, whatever it may be, should be reduced or discontinued for a few days when the appearance of muscular twitching indicates that the therapeutic limits are reached.

The treatment of partial paralysis calls for the administration of doses of 0.003 gm. ($\frac{1}{20}$ grain) three or four times a day for ten days, with an interval of a week before continuing it. Halsey states that at least that amount must be given to overcome depression of the central nervous system, especially in infectious diseases.

Poisoning by hydrated chloral, alcohol, chloroform and other narcotics may be treated with an initial intramuscular injection of 0.004 gm. ($\frac{1}{16}$ grain); if this causes an improvement in the respiration the dose may be repeated in about two hours if necessary, but if the strychnin adds to the depression, or if there is no improvement with that dose, caffeine should be used, and, as stated previously, it probably should be used from the beginning. Morphin interferes with the movements of the stomach, and since strychnin is probably not absorbed readily from the human stomach, it should not be administered orally in the treatment of morphin poisoning, but intramuscularly, to secure quick action, and later by the rectum if desired.

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Strychnin salts are absorbed readily from the gastro-intestinal tract under normal conditions, and from the subcutaneous tissues, the dose being approximately the same whether it be given by mouth, rectum or subcutaneously. In emergencies its action may be elicited almost instantaneously after intravenous injection, but the dose by this method of administration is only about half the oral dose.

Some authors state that large doses of strychnin may lead to toxic symptoms through cumulation, because of the slow elimination, but there is no danger of serious poisoning to be feared when the daily dosage is limited to 0.010 gm. ($\frac{1}{6}$ grain), and the administration stopped on the appearance of increased reflexes.

MATERIA MEDICA

Nux Vomica, U. S. P., the seed of *Strychnos Nuxvomica*, an oriental tree, at present comes chiefly from India and Ceylon. The fruit, a berry, is of the size and appearance of an orange, and contains usually from two to five of the flat circular seeds embedded in a mucilaginous pulp. The seeds are hard and extremely tough.

The drug is probably the most widely used (and abused) article in our materia medica, and with its alkaloid, strychnin, it is prescribed more frequently even than opium and its alkaloids and derivatives.

Nux vomica contains about 1.25 per cent. of strychnin. It also contains brucin, an alkaloid which resembles strychnin somewhat in its actions, but which is of little importance, as it contributes little to the action of the crude drug. *Nux vomica* also contains an unimportant glucosid, loganin, and tannin similar to that occurring in coffee.

Nux vomica is seldom administered in substance, one of the galenical preparations being usually preferred.

Extractum Nucis Vomicae, U. S. P., a powdered extract which contains 5 per cent. of strychnin, is usually employed in the form of a pill or capsule,

frequently combined with iron and quinin, as a bitter tonic.

It may be prescribed somewhat as follows:

R	Extracti nucis vomicae.....	gm. 0 4	gr. vi
	Ferri reducti.....	2 5	gr. xl
M. et fac pilulas xx.			
One pill 3 or 4 times a day.			

Or as follows:

R	Extracti nucis vomicae.....	gm. 0 4	gr. vi
	Quininae sulphatis.....	2 0	gr. xxx
	Ferri reducti.....	2 0	gr. xxx
M. et fac capsulas xx.			
One capsule to be given 3 times a day.			

Tinctura Nucis Vomicae, U. S. P., is the more generally useful of the preparations of nux vomica, and is administered preferably diluted with water, or with water and syrup or fruit-juice at the time the dose is taken.

Tincture of nux vomica represents 10 w/v per cent. of the drug in a mixture of alcohol and water.

Strychnina, *Strychninae Nitrates* and *Strychninae Sulphas*, U. S. P., are the three forms in which strychnin is official. They are colorless crystals or white powders, having an intensely bitter taste, which is perceptible in solutions containing 1 part of the alkaloid or its salt in 700,000 parts of water.

Strychnin and its salts may be administered in the form of pills, capsules or cachets, when the bitter taste is not desired. It is seldom administered by the rectum, but it is absorbed readily and may be given in the form of suppositories. It may be given hypodermically when for any reason the oral or rectal administration is contra-indicated, or when rapidity of action is essential; and in urgent cases it may be given intravenously in physiologic salt solution, of course, with the proper technic.

The sulphate is soluble in 31 parts of water and in 65 parts of alcohol; the nitrate in 42 parts of water, and in 120 of alcohol; the alkaloid is only slightly soluble in water, requiring 6,400 parts for solution; it is soluble in 110 parts of alcohol.

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The salts are precipitated by the usual precipitants of alkaloidal salts, including alkalies, alkali carbonates, and by the bromids and iodids. Combinations of strychnin salts with precipitants in solution should be avoided, as the precipitate might escape detection and nearly the whole amount be taken in the last dose.

ATROPIN

Atropin is much the most important member of its group, which includes scopolamin and homotropin and the crude drugs, belladonna, hyoscyamus and stramonium, together with their preparations. The alkaloids of this group are commonly called the mydriatic alkaloids, because dilatation of the pupil is the most characteristic action which they possess in common. While they exhibit individual differences in their actions, they form a fairly well-defined group.

The action of atropin will be discussed in some detail, and the special uses of others will be mentioned, but in the main it is to be understood that the several drugs are used for the same purposes, with the exception of scopolamin. This drug occupies a special field of usefulness because of the fact that while it resembles the other members in a general way, its stimulant action on the central nervous system is so much less pronounced than theirs, while the depression it produces is so much more prominent, that it is used to produce depression, while atropin is used to cause stimulation. This illustrates the difficulty of classifying drugs satisfactorily.

The chemical investigation of the drugs which yield the mydriatic alkaloids presents many difficulties, and some confusion has resulted from the application of the same name to different substances, and of different names to the same substance in slightly different degrees of purity. It is recognized at present that the substance first described as hyoscin was nothing but an impure form of the alkaloid which in pure form was first described correctly under the name of "scopolamin;" hence the two terms are purely synonymous, and only the name "scopolamin" should be used.

Therapeutic doses of atropin exert a greater action on the medulla than on the brain, but with toxic doses the effects on the cerebrum become more pronounced.

Atropin stimulates the respiratory center in the medulla, causing a marked increase in the amount of air breathed in a given period of time. Poisonous doses cause depression of the respiratory and other centers. This action on the respiratory center is of great importance, atropin being one of the most active of the respiratory stimulants which we have.

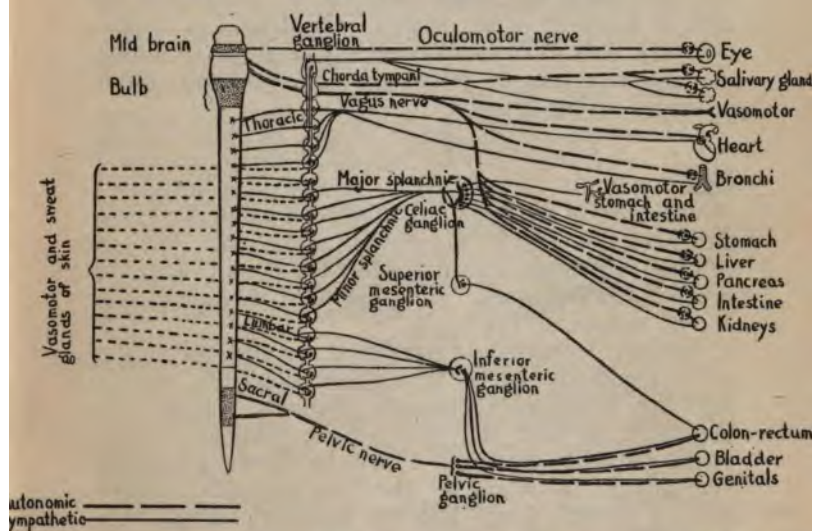


Diagram of the anatomic relations of the autonomic and sympathetic systems (from Meyer and Gottlieb, *Experimentelle Pharmakologie*, 1911, p. 128).

The vasomotor centers are stimulated by moderate doses of atropin, which cause a scarlet appearance of the face and upper part of the body, due to a dilatation of the vessels of those regions simultaneously with a constriction of the vessels of the splanchnic region. There may be merely a redness of the skin, or there may be a rash, followed by desquamation, but usually the rash disappears within a short time.

The vasoconstriction tends to raise the blood-pressure, but the effects of atropin on the circulation

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are complex and changes in the blood-pressure with small doses depend on the heart-rate rather than on any vasoconstriction.

The vagus center is stimulated somewhat with the respiratory and vasomotor centers, but this is soon overshadowed by the depression or paralysis of the vagus endings in the heart, which is one of the characteristic actions of all of the mydriatic alkaloids.

Nausea and vomiting are mentioned among the symptoms of poisoning by atropin; dogs, however, do not show these symptoms after the intravenous injection of large or small doses of the drug, but on the contrary, only very small doses are required to inhibit the emetic action of pilocarpin and, probably, other centrally acting drugs.

The actions on the brain cannot be described in detail, and it need only be said that larger doses cause stimulation of certain areas, resulting in increased coordinated movements, talkativeness, excitement and delirium, followed by depression and coma. Atropin in moderate doses does not affect the psychic areas so much as caffein does. It is not used therapeutically for its actions on the brain.

Atropin depresses or paralyzes the endings of the parasympathetic³ nerve throughout the body, including the oculomotor, chorda tympani, vagus and erigens, and also the sympathetic endings in the sweat-glands in the skin. It will be observed that the sympathetic endings in the sweat-glands behave toward several drugs like the parasympathetic endings (Fig. 1).

A discussion of the peripheral actions of atropin is largely a discussion of the functions of the parasympathetic nerves, for atropin simply abolishes those functions, but it acts on these endings in different parts of the body with varying degrees of intensity.

3. Reference to Figure 1, taken from Myer and Gottlieb's *Pharmacology*, Ed. 2, will show the relationship between the sympathetic and parasympathetic nerves. Epinephrin stimulates the myoneural junctions of all of the sympathetic nerves (except those to the vessels and sweat-glands of the skin), while it leaves those of the parasympathetic unaffected. Atropin, on the other hand, paralyzes the endings of those nerves which epinephrin does not affect while it has no influence on those which epinephrin stimulates. Many other drugs show similar selective actions with reference to these nerves.

Hence a given dose does not have the same relative effect on all organs which the nerves supply.

Atropin can be brought into contact with the oculomotor endings by dropping a solution into the eye, without inducing its systemic actions, but its actions on other parasympathetic endings cannot be elicited so conveniently.

Depression of the oculomotor endings causes dilatation of the pupil through the unopposed actions of the radiating fibers, and it also causes paralysis of the muscle of accommodation. These actions are prolonged after repeated applications, or after the use of strong solutions, and it may be a week or more before the eye becomes quite normal.

The action of homatropin on the pupil is qualitatively like that of atropin, but the effect is not so lasting. Homatropin is often preferred when an examination of the eye is to be made, but it is not so dependable as atropin, which many oculists continue to use even for the examination of the eye. Dilatation becomes maximal in a period usually varying from half an hour to an hour. Scopolamin acts as a mydriatic in the same way as atropin.

The actions of atropin on the pupil and on accommodation may be counteracted with physostigmin, but this renders the muscles of accommodation hyperexcitable, so that efforts at accommodation result in spasm of the muscles, and reading is attended with discomfort.

Paralysis of the chorda tympani endings interferes with the secretion of the salivary glands, rendering the mouth and throat dry, the voice hoarse, and swallowing difficult. The mucous glands in the nose and respiratory passages and the gastric, pancreatic and biliary secretions, and possibly the secretion of milk, are also inhibited by atropin. The action on the sympathetic endings in the sweat-glands causes the skin to become dry, these being the only sympathetic endings which behave toward a number of drugs like the parasympathetic.

The paralysis of the vagus endings in the heart causes the heart to beat more rapidly; in the stomach and intestine it overcomes the motor influence of the vagus.

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The lower part of the colon, the rectum and the uterus are innervated by the erigens, the endings of which atropin paralyzes. The intestinal effects will be discussed in connection with the evacuants.

Depression of the vagus endings in the bronchi result in muscular relaxation, when the muscles are spasmodically contracted in asthma.

Atropin depresses the sensory endings in the skin with which it may be brought into contact in the form of an oleate, or of an ointment of belladonna extract.

Atropin and the other mydriatic alkaloids are absorbed promptly from the gastro-intestinal tract and from the subcutaneous tissues. Some absorption occurs even from the unbroken skin when suitable application is made; at least the drug may reach the sensory endings in sufficient amount to cause analgesia.

The mydriatic alkaloids are excreted in the urine for the greater part, and scopolamin is said to be excreted in human milk to a slight extent.

The fatal dose of atropin is supposed to be about 125 mg. (2 grains), but much smaller amounts give rise to unpleasant and even alarming symptoms of poisoning. These symptoms may be enumerated somewhat in the order of their occurrence with increasing doses as follows: Even the larger therapeutic doses induce redness, or rash of the skin, which results in desquamation; the skin, as well as the nose, mouth, throat and bronchi become dry; the voice becomes hoarse, swallowing difficult; the heart becomes rapid with rise of blood-pressure, and some motor unrest. Talkativeness, and dilatation of the pupils from systemic action occur only with very large doses; these symptoms may be succeeded by coma and respiratory failure ending in death, or there may be convulsions; nausea and vomiting are reported as common symptoms, and these must be of central origin. Small doses of atropin, however, prevent nausea when given with morphin, and even the largest doses of atropin do not cause vomiting after intravenous injections in dogs.

There is an extraordinary difference in the degree to which different patients react to atropin. One will respond to the smallest therapeutic dose with dryness of the throat and redness of the skin, while another may take the maximum dose usually advised with little inconvenience. An instance has been reported in which a woman took about an ounce of a 15 per cent. tincture of belladonna, in a mixture containing half as much fluidextract of hyoscyamus, daily for several days with no other symptoms than slight dryness of the throat. If the preparations used were of full strength, the patient must have received approximately half a grain (30 mg.) of mydriatic alkaloids daily. Incomplete absorption probably explains the want of toxic symptoms in this case.

Poisoning by atropin may occur through the accidental taking of a solution intended for external use, or the use of strong solutions in the eye. Belladonna berries are attractive in appearance and are not infrequently eaten by children. Fortunately, they are indigestible and may result in vomiting before a fatal dose has been absorbed.

The symptoms of poisoning by atropin or one of the members of the group are usually so typical as to direct attention to the cause, but where the earlier symptoms are obscure, suspected poisoning may be confirmed by testing the urine for atropin. For this purpose a few drops of the urine are dropped into the eye of a cat; if atropin or any other of the mydriatic alkaloids is present the pupil will dilate widely within about half an hour. The test should be made within thirty-six hours after the poison has been swallowed.

In case of poisoning by the berries, or when one suspects that a poisonous dose of one of these alkaloids remains in the stomach, recourse should be had at once to the stomach-tube. Tannin or potassium permanganate may be added to the water used in washing the stomach, but the use of alkaloidal precipitants or of potassium permanganate does not obviate the necessity of emptying the stomach, for the precipitated alkaloid would be absorbed, though more

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slowly than the soluble salt, and one cannot be certain that the potassium permanganate has been brought into contact with all of the alkaloid. Excretion should be hastened through the use of diuretics, hot water and tea, and in urgent cases the intravenous injection of normal salt solution under suitable precautions would be justified.

Excessive doses of atropin or the other mydriatic alkaloids may prove fatal in a short time, but such amounts are seldom taken, and the physician is more frequently called on to treat the alarming symptoms which yield to treatment.

Pilocarpin stimulates the salivary and mucous glands, and relieves the dryness of the mouth and throat; morphin is useful only in the early stages of poisoning by atropin, not at all in scopolamin poisoning, in which it is directly contra-indicated.

If depression has already begun in atropin poisoning, or if the dose taken was sufficient to lead one to expect severe depression later, morphin is contra-indicated, or at most small doses should be used in the stage of excitement. Application of cold water or of the ice-bag to the head is useful during delirium. Respiratory failure demands artificial respiration, and in such cases vigorous means should be adopted to secure rapid elimination by intravenous injections of normal salt solution.

THERAPEUTIC USES

Atropin is useful as a respiratory stimulant in various conditions. It is often recommended in the treatment of morphin poisoning, but authorities differ widely in their views concerning the wisdom of this measure, and to a greater extent in regard to the dose which should be employed in any event. Atropin and morphin in small doses are antagonistic in their actions on the respiratory center, but they are synergistic in large doses, both causing depression. The difference in opinion results from the question whether atropin is capable of causing stimulation without subsequent depression, and if this be possible, the next question concerns the amount which can be given without causing severe depression.

It seems probable that moderate doses of atropin are useful in combating the action of a poisonous dose of morphin on the respiratory center, because there seems to be little danger of serious depression from such doses of atropin. The amount which can be given in such cases can hardly be stated in exact figures. If used for this purpose, it is best given in doses of about 1 mg. ($\frac{1}{60}$ grain). This is repeated every hour until three doses are given if each of the first two doses is followed by improvement in the respiration. This probably represents the maximum that can be given with safety, within a period of six hours. Caffein is safer than atropin and probably deserves the preference in all cases in which respiratory stimulation is required.

Atropin probably deserves to be used more frequently than it is in shock, because it is capable of increasing the heart-rate, when this is unduly slow, and this, with the action on the vasomotor centers, tends to increase the blood-pressure, and the stimulation of the respiratory center should further improve the condition. It would appear to be useful in respiratory and circulatory failure during anesthesia, for, according to Hewitt, cardiac failure during anesthesia is frequently secondary to interference with respiration.

Its use before the administration of chloroform will prevent the dangerous inhibition of the heart which sometimes occurs early in the course of the administration, before the heart is seriously injured by the direct action of the chloroform.

The therapeutic use of atropin as a mydriatic has been indicated in discussing its action on the pupil. It appears to be more certain than homatropin in causing complete paralysis of accommodation, but the latter is preferable as a mydriatic when there is reason to fear glaucoma, because it does not increase the intra-ocular tension so much as atropin. The prolonged action of atropin is preferred in iritis to prevent adhesions and to break up those already formed.

Excessive salivation, sweating from various causes, such as the use of large doses of the antipyretics, and

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the night sweats of phthisis may be controlled by very small doses of atropin. The application of ointment of atropin or belladonna does not appear to relieve local sweating. Its continued local application to the breast diminishes the flow of milk.

Atropin is used to increase the heart-rate, especially where this is abnormally slow (bradycardia) owing to overactivity of the vagus, but it has much less influence on the rate when this is due to cardiac disease, and when slow rhythm is due to heart-block atropin will not influence the rate. Certain forms of cardiac irregularities due to vagus control are abolished by atropin. Its action on the vagus is much less effective at the extremes of life because the vagus itself has less control over the heart-rate in the young and the aged than during the remainder of life.

Bronchial asthma resulting from spasm of the muscles is often relieved by atropin or one of the crude drugs of this group.

Atropin abolishes spasmodic contraction of the pylorus, and is useful in the treatment of lead colic in which spasm of the muscles of the intestine occurs, and in the same way it is useful in spasm of the muscles of the ureter and of the bile-ducts due to the irritation of calculi.

Atropin is useful in relieving certain neuralgias for which it is commonly applied locally.

Belladonna is used in whooping-cough, in which Cushny suggests that it may allay the excitability of the respiratory center.

Atropin is the physiologic antagonist of those poisons which exert their actions through stimulation of the parasympathetic (vagus, oculomotor, chorda, erigens) nerves, such as physostigmin, pilocarpin and muscarin, but it is not feasible to discuss in detail its actions in antagonizing these poisons. It has been found that animals survive a larger dose of aconitin if atropin be administered than without it. The cardiac effect of aconitin is attributable to vagus influence in part.

Drugs of the atropin group have long enjoyed a special reputation in the treatment of nocturnal enuresis in children, but there is no doubt that they

have been used with little discrimination in many cases. Unfortunately, the causes of this condition are not sufficiently understood to enable one to say just when atropin will be useful. Under the circumstances it may be tried when hygienic measures have proved unavailing, but it should not be employed for any considerable period when it does not prove unmistakably useful.

There is no reason to suppose that all cases of nocturnal enuresis arise from the same cause, or that they can be relieved by the same treatment; but it is probable that when it results from an abnormally active reflex operating through the parasympathetic nerve to the bladder, atropin, or one of the other members of the group, may afford relief.

Hyoscyamus is sometimes preferred, probably acting better than belladonna in those cases in which nervousness plays an important rôle.

Occasional wetting of the bed by children probably results in some cases from delayed absorption of fluids from the alimentary canal and increased secretion of urine at such time as the sweat-glands of the skin are less active than usual. Atropin would probably aggravate the trouble in such cases.

The recommendation of drugs with such diverse actions as ergot, cantharides, buchu, rhus aromatica, strychnin and arsenic by a prominent writer serves to indicate the vagueness of our knowledge of this condition.

If belladonna or other drug of this group is used it is preferable to employ fairly large doses at once and abandon it if it does not afford prompt relief.

Hyoscyamus is generally reputed to be more useful than belladonna and stramonium as a sedative to the nervous system; stramonium is little used except as an ingredient of asthma powders, used for smoking.

Scopolamin hydrobromid has a special field of usefulness in quieting the excitement of the insane and producing sleep. It is more effective when given at night than during the day.

Some ophthalmologists prefer it to atropin as a mydriatic, because it is said to be less irritating and

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to produce a brief but complete dilatation of the pupil with paralysis of accommodation.

Its use with morphin in producing narcosis will be discussed after morphin has been considered.

Extract of belladonna is sometimes applied to the skin in the form of an ointment for the relief of neuralgic pain and for acute inflammatory conditions; the commercial belladonna plaster is widely used by the laity, but it is doubtful whether the belladonna contributes anything to the effect.

It is probable that all of the crude drugs and galenical preparations of this group are superfluous, and that with a better knowledge of the actions of atropin and scopolamin these alkaloids will replace the crude drugs and their galenical preparations as completely as quinin has displaced cinchona and its galenicals.

DOSAGE

The average dose of atropin sulphate is stated to be 0.4 mg. ($\frac{1}{150}$ grain), but there are many conditions for which this dose would be insufficient and others for which it would be too large.

The dose should be carefully graduated for the specific purpose for which the drug is intended, as one can then accomplish the desired effect with a minimum of side actions.

The smallest therapeutic doses of atropin commonly used are probably those which are added to the laxatives. The official compound laxative pill contains 8 mg. ($\frac{1}{8}$ grain) of extract of belladonna, or approximately $\frac{1}{10}$ mg. ($\frac{1}{650}$ grain) of atropin. The largest doses commonly used internally are employed for relieving spasm of the intestinal muscle, in which case as much as 3 mg. ($\frac{1}{20}$ grain) may be needed.

To lessen sweating the dose is $\frac{1}{4}$ mg. ($\frac{1}{250}$ grain); to paralyze the vagus endings in the heart, 1 mg. ($\frac{1}{60}$ grain); to antagonize morphin poisoning, 1 to 3 mg. ($\frac{1}{60}$ to $\frac{1}{20}$ grain); but, as previously stated, there is considerable diversity of opinion concerning the advisability of the larger dose given here; to antagonize other poisons, such as aconite, pilocarpin, and other drugs which stimulate the autonomic nerves,

the dose required will depend on the action elicited by the poison; since aconite stimulates the vagus, this should be paralyzed by atropin, and about 1 to 1.5 mg. ($\frac{1}{60}$ to $\frac{1}{40}$ grain) should be used. Pilocarpin induces excessive secretion of the bronchial and salivary glands, the excessive bronchial secretion constituting a danger with overdoses of pilocarpin, and to antagonize this, 0.5 mg. ($\frac{1}{125}$ grain) atropin should be used.

Atropin is more effective in antagonizing pilocarpin than is pilocarpin in antagonizing atropin. Some persons appear to be remarkably susceptible to the action of atropin in inducing skin rashes. Dryness of the throat is commonly induced by doses of 1 mg. ($\frac{1}{60}$ grain) or over.

A dose of 0.2 mg. ($\frac{1}{300}$ grain) is said to stop the vomiting which small doses of morphin cause in susceptible persons.

Asthma resulting from spasm of the bronchial muscle, whatever the exciting cause, may be relieved by atropin in doses of 0.25 to 0.5 mg. ($\frac{1}{250}$ to $\frac{1}{125}$ grain), repeated several times daily if necessary.

Belladonna and other members of the group are used in the form of cigarets for the relief of asthma. It is stated that the smoke of 4 gm. (60 grains) of stramonium in the form of a cigaret contains 0.4 mg. ($\frac{1}{150}$ grain) atropin.

Children bear atropin fairly well, and relatively large doses are frequently recommended in the treatment of whooping-cough, and such large doses are required if the depression of the respiratory center is the object to be attained.

As little as 1 drop of a 1:1,000 solution of atropin dropped into the eye will cause dilatation of the pupil, but stronger solutions are required to paralyze the muscles of accommodation, and 1 per cent. solutions are commonly employed for this purpose.

The average dose of scopolamin hydrobromid is 0.5 mg. ($\frac{1}{125}$ grain); much larger doses are sometimes required for quieting the insane, but even here caution must be shown for it may cause depression of respiration and a rapid fall in the blood-pressure, resulting in collapse.

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For use as a mydriatic alone solutions of from 1:500 to 1:1,000 suffice, but where paralysis of accommodation is required, somewhat stronger solutions are necessary (from 1:100 to 1:250).

The average doses of the galenical preparations of the drugs of this group will be given in the discussion of the materia medica.

English authorities advise doses of the drugs of this group which we are accustomed to consider enormous; for example, Leonard Guthrie states that in the treatment of habitual nocturnal enuresis tincture of belladonna should be pushed to full doses, that is, to from 10 to 40 minims for a child of 10 to 12 years. The British tincture of belladonna is required to contain from 0.048 to 0.052 per cent. of alkaloid, or about 50 per cent. more than is required by the U. S. P.

Such doses may prove beneficial in cases of habitual nocturnal enuresis when the treatment in vogue in this country would fail, but such heroic treatment will certainly result in dryness of the throat, rashes and other disagreeable side actions and should not be used except in persistent cases when milder treatment has failed.

One will find formulas prescribing the drugs of this group in text-books which do not take into account the fact that the alkaloids of this group are prone to undergo changes and that we cannot foretell what changes will take place when one of the galenical preparations is mixed with alkaline salts and allowed to stand. A prescription of this nature found in a standard work on therapeutics includes tincture of belladonna, potassium iodid, ammonium carbonate, potassium bicarbonate, camphor water and water.

Any tincture of this group is prescribed preferably alone except that it should be diluted (and flavored, if desired) so that the dose may be measured conveniently. The following illustrates the method of prescribing tincture of belladonna:

	c.c.	
℞ Tincturae belladonnae.....	4	℥ 3i
Syrupi aurantii.....	15	℥ 3iv
Elixiris aromatici....q. s. ad	30	℥ 3i
M. Dose: a teaspoonful.		

The smoke of burning belladonna and stramonium leaves has been widely used by inhalation for the relief of asthma. The leaves are ground or granulated in order to prevent their burning with a flame, and a little potassium nitrate is commonly added to secure more uniform combustion. The mixture is burned on a plate, smoked in a clean pipe, or used in the form of cigarets.

W. J. Hadley advised the use of a mixture of equal parts of belladonna, hyoscyamus, and stramonium leaves and potassium nitrate as a fumigation, but there is no advantage in using a mixture of drugs containing such similar constituents, and any one of the leaves may be used with the addition of from one-eighth to one-fourth its weight of potassium nitrate. Half a teaspoonful of the mixture is used at each fumigation.

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Atropina.—Atropin, U. S. P. An alkaloid obtained from *Atropa belladonna* and from other solanaceous plants. It occurs as colorless crystals or as a white crystalline powder, odorless and having a bitter nauseating taste. Atropin in all its forms is usually contaminated with a small amount of optically active hyoscyamin. The alkaloid is only slightly soluble (1:450) in water but freely soluble (1:1.5) in alcohol. It is usually prescribed in the form of:

Atropinae Sulphas.—Atropin Sulphate, U. S. P.

This salt occurs as a white crystalline powder that is odorless and has a very bitter and nauseating taste. It is permanent in air and very soluble (1:0.4) in water, and (1:4) in alcohol.

Scopolaminae Hydrobromidum.—Scopolamin Hydrobromid, U. S. P. This is sometimes called "hyoscin hydrobromid," though the latter name was originally applied to an impure product. Scopolamin hydrobromid occurs as colorless crystals, odorless and having an acrid slightly bitter taste. It is freely soluble (1:15) in water and (1:16) in alcohol.

Homatropinae Hydrobromidum. — Homatropin Hydrobromid, U. S. P. The hydrobromid of an alka-

loid, tropin mandelate, produced synthetically. The alkaloid was discovered in 1879 by Ladenberg in the course of his researches on the constitution of atropin. It is used extensively in ophthalmologic practice and appears to be more stable than atropin in aqueous solution. It is seldom given internally, though it has been used in doses of from 0.5 to 3 mg. ($\frac{1}{100}$ to $\frac{1}{20}$ grain).

Belladonnae Folia.—Belladonna Leaves, U. S. P. The dried leaves of *Atropa Belladonna*, which are required to yield by the pharmacopeial process not less than 0.3 per cent. of mydriatic alkaloids. Belladonna leaves are rarely administered as such; the more widely used preparations of this drug are:

Tinctura Belladonnae Foliorum.—Tincture of Belladonna Leaves, U. S. P. Each 100 c.c. of this preparation represents the soluble constituents of 10 gm. of the drug in diluted alcohol and should contain 0.03 gm. of the alkaloids from belladonna leaves. The average dose is 0.5 c.c. (8 minims).

Extractum Belladonnae Foliorum.—Extract of Belladonna Leaves, U. S. P. A hydro-alcoholic extract of belladonna leaves which should contain 1.4 per cent. of mydriatic alkaloids. The average dose is 0.01 gm. ($\frac{1}{8}$ grain).

The average doses of the tincture and the extract of belladonna represent only about $\frac{1}{8}$ mg. ($\frac{1}{400}$ grain) of total alkaloids, which is much less than the average dose of atropin for many of the purposes for which it is used.

Unguentum Belladonnae.—Belladonna Ointment, U. S. P. An ointment containing 10 per cent. of extract of belladonna leaves in a mixture of hydrous wool fat and benzoinated lard.

Emplastrum Belladonnae.—Belladonna Plaster, U. S. P. Represents approximately 30 per cent. of extract of belladonna leaves, and should contain not less than 0.38 per cent. and not more than 0.42 per cent. of mydriatic alkaloids. All plasters of belladonna and allied drugs are necessarily of doubtful utility because the drug itself is probably effectually sealed and prevented from being absorbed

by the rubber with which it is mixed. The use of rubber base plasters for any other purpose than support is not justified by experimental observations.

Hyoscyamus.—*Hyoscyamus*, U. S. P. This drug, commonly called henbane, consists of the dried leaves and flowering tops of *Hyoscyamus niger*. The only preparation of it that is at all extensively used is:

Tinctura Hyoscyami.—Tincture of *Hyoscyamus*, U. S. P. One hundred c.c. of this tincture represent the soluble constituents of 10 gm. of *hyoscyamus* in dilute alcohol and should contain approximately 0.007 gm. of mydriatic alkaloids, chiefly *hyoscyamin* and *scopolamin*. It is usually given in doses of from 0.5 to 2.0 c.c. (10 to 30 minims).

Stramonium.—*Stramonium*, U. S. P. The leaves of *Datura Stramonium*, commonly called Jamestown or jimson weed. Its constituents are much the same as those of belladonna.

LOBELIA

The action of lobelia is practically that of its alkaloid, lobelin, which resembles nicotin closely in its physical properties and actions.

Tobacco was used formerly in a great variety of conditions, but owing to its careless use and the great toxicity of its alkaloid, many accidents resulted, and it fell into disuse in therapeutics. If the drug which has been studied more frequently should now be considered of little value, it is difficult to explain the advantages to be derived from lobelia. Lobelia itself is no longer used as an emetic as it was formerly, but it would seem that physicians are loath to give up a drug which has been so long in use.

Those who wish a detailed description of lobelia, or lobelin, are referred to the larger text-books of pharmacology, for its actions are very complex. The peripheral actions of lobelin, like those of nicotin, may be summarized as consisting of stimulation of the ganglia of the sympathetic and parasympathetic systems throughout the body after small doses, followed by depression or paralysis of these ganglia with large doses. It will thus be seen that lobelin acts on the

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organs innervated by the sympathetic and parasympathetic systems in opposite directions, depending on the dose, and the complex nature of its effects may be appreciated when one remembers that the actions of these two sets of nerves are commonly antagonistic.

Stimulation and depression of the ganglia induce the same effect on the organ supplied as stimulation and depression of the nerve endings; hence lobelin combines in itself the peripheral actions of a number of drugs including atropin, pilocarpin, epinephrin and others. In addition to these actions it stimulates and later depresses various parts of the central nervous system.

The emetic action, for which lobelia was formerly used, points toward the medullary centers as the seat of this stimulation, and it also stimulates the vagus, vasomotor and respiratory centers.

The action on the vagus ganglia results in cardiac slowing, which is augmented by the stimulation of the vagus center, but this is soon followed by an increased heart-rate due to the depression of the ganglia. The rise of blood-pressure of peripheral origin is also augmented by the central actions.

Lobelia is not used for these effects, and it is now sought to avoid more than slight stimulation of the vomiting center, because dangerous collapse is frequent with large doses.

The treatment of poisoning is symptomatic, severe poisoning with lobelia being rare since its use as an emetic has been abandoned.

Nicotin is excreted by the kidneys in part, and the same is probably true of lobelin.

THERAPEUTIC USES

The principal therapeutic use of lobelia is in asthma, in which it is sought to utilize the paralysis of the vagus in the bronchi. It is not apparent that it has any decided advantages over the mydriatic alkaloids for this purpose, especially as the action of atropin has been found to be more lasting. Lobelia is sometimes used as an expectorant, in which case the nauseant stage should not be exceeded. So-called cardiac

asthma, or the presence of severe cardiac disease complicating spasmodic asthma, is a contra-indication for lobelia.

DOSAGE

The herb is seldom employed as such, the tincture being used in doses of 0.5 to 1.5 c.c. (10 to 20 minims).

MATERIA MEDICA

Lobelia.—*Lobelia*, U. S. P. The dried leaves and tops of *Lobelia inflata*. It is still widely used in eclectic practice.

Tinctura Lobelia.—Tincture of *Lobelia*, U. S. P. Each 100 c.c. represents the soluble constituents of 10 gm. of the drug in diluted alcohol.

CAMPHOR

We are unable to offer a rational basis for all the therapeutic uses to which camphor is put, its exact mode of action being unknown, but it is often used as a stimulant of the vasomotor centers, partly as a result of clinical experience and partly on the basis of the results of experiments on animals.

The effects of very large doses of camphor resemble those of picrotoxin so far as the stimulant actions on the medulla are concerned, but there is an essential difference in that even moderate doses of the drugs of the picrotoxin group tend to cause depression after the stimulation has passed, whereas with camphor, depression becomes of importance only after extremely large amounts.

The convulsions which are seen after massive doses of camphor have been administered to animals (cats or dogs) are usually attributed to the action on the medulla, but it is probable that other parts of the central nervous system are also concerned in this action, especially in young animals. The convulsions are epileptiform in character.

Moderate doses of camphor stimulate the respiratory center, and while doses comparable to those used in therapeutics have little influence on the respiratory and vasomotor centers, in normal animals, it is quite possible that those centers may be influenced more

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easily by camphor, as in other drugs, when they have been previously depressed. It will be recalled that doses of strychnin less than those causing marked hyperexcitability have little influence on the normal blood-pressure, and that even convulsive doses cause only a brief, though high, rise of pressure in the normal animal.

Clinical experience seems to show that camphor is sometimes useful in improving the respiration and circulation when collapse is impending, and that it also acts beneficially on the heart, but there are many diametrically opposed observations recorded concerning its clinical value.

Camphor is widely used in Europe for its circulatory actions, especially in threatened cardiac failure, but on the other hand, certain English observers have recently reported that they were unable to detect any constant influence on the circulation after the subcutaneous injection of much larger doses than those commonly used.

It seems probable that camphor may cause some change in the distribution of the blood by constriction of the vessels in one area and simultaneous dilatation of those in another, without increasing the pressure.

It is quite possible that much of the diversity of opinion arises from differences in the methods of employing the drug, both as to the selection of cases in which it is to be used and in the mode of administration.

Camphor resembles the drugs of the picrotoxin group further in that it is absorbed somewhat irregularly, or at least, the actions are elicited to a variable degree after the administration of a given dose, and this probably depends on differences in the ratio of absorption and excretion.

It has been observed in laboratory experiments that the results were somewhat more nearly uniform after the oral administration of camphor dissolved in olive oil than when it was given subcutaneously, but the two modes of administration gave only slightly different results. It is probable that the effects may be elicited most rapidly by means of the intraperitoneal

injection of camphor dissolved in ether, but there are mechanical difficulties involved in the injection, because of the extreme volatility of ether. The method is not recommended.

THERAPEUTIC USES

Camphor is used like other respiratory stimulants, and in collapse for its action on the respiration and circulation, and, as stated, in impending cardiac collapse. It has long been popular in combination with other drugs to promote sweating, and enjoys a certain degree of popularity in the treatment of "colds." It is not commonly used now in this way by physicians.

DOSAGE

Camphor is frequently administered internally in doses of from 0.1 to 0.3 gm. (2 to 5 grains) preferably in the form of capsules, cachets, mixtures or solutions. Camphor water, a comparatively weak solution, is given in doses of 15 c.c. (4 fluidrams). Spirit of camphor, a 10 per cent. alcoholic solution, which is the most frequently used preparation of camphor, can be given on sugar, cracked ice or mixed with cold water in doses of from 0.5 to 1.5 c.c. (7 to 20 minims). The liniment of camphor, which as its name indicates is primarily intended for external use, though it is double the strength of the foregoing, can be given in approximately the same dose. It may be directed in the form of an emulsion. It is frequently used for hypodermic administration. A more limpid preparation for the latter purpose can be made by directing the use of oil of sweet almond or olive oil in place of the cotton-seed oil used in the official preparation.

MATERIA MEDICA

Camphora.—Camphor, U. S. P. The official product is described as the dextrogyrate modification of the saturated ketone obtained from *Cinnamomum Camphora*, purified by sublimation. The drug occurs in commerce as white, translucent masses of a tough consistency and crystalline structure; it may be powdered readily with the aid of a small amount of alcohol. Camphor has a characteristic odor and pungent taste.

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It is very slightly soluble (1:700) in water, but freely soluble (1:3) in alcohol and (1:4) in olive oil and other fatty oils of this type. The several official solutions include:

Aqua Camphorae.—Camphor Water, U. S. P. The saturated solution of camphor and distilled water. This is a weak preparation used chiefly as a vehicle for collyria.

Spiritus Camphorae.—Spirit of Camphor, U. S. P. An alcoholic solution of camphor (10 gm.) in alcohol (to make 100 c.c.).

Linimentum Camphorae.—Camphor Liniment, U. S. P. Popularly known as camphorated oil. It is a solution of camphor (20 gm.) in cottonseed oil (enough to make 100 c.c.).

CAFFEIN AND THEOBROMIN

Caffein and theobromin belong to a group of substances which are commonly known as the purins, from the fact that they contain a purin nucleus. Xanthin is dioxypurin, and theobromin and caffein are dimethylxanthin and trimethylxanthin, respectively. Another dimethylxanthin, theophyllin, occurs in the leaf of the tea; it has been prepared synthetically and called theocin.

Comment has often been made on the extraordinary extent to which plants which contain caffein are used among nearly all civilized peoples and even among savages, which is all the more remarkable in view of the fact that there is nothing in the taste of these plants which serves to direct attention to them. It is well known that savage tribes are constantly on the alert for new poisons, and when a caffein-bearing plant is tested the psychic effects of caffein on any one who has not used it previously could hardly fail to attract attention, and lead to the further use of the plant.

Caffein does not increase the functions of the normal brain under the best conditions for mental work, that is, after sound and refreshing sleep and sufficient rest with freedom from worry, but when small doses are used after severe physical or mental effort it

causes fatigue to disappear, and the perception of sensory stimuli and the association of ideas are promoted.

A good illustration of the inability of caffein, or other drug, to improve the best of normal conditions is afforded by the experience of athletes who find that caffein tends to lessen, rather than increase, their performances.

Large doses of caffein interfere with the proper association of ideas; for example, students are unable to study so effectively after large doses as without them. With very large amounts there is actual confusion of thought with ringing in the ears, flashes of light and other signs of mental disturbance. There is also restlessness due to stimulation of the motor areas, and to heightened reflexes in the brain and cord, and with excessive doses there are convulsions similar to those seen in fatal poisoning with strychnin, and death follows from respiratory or cardiac failure.

Caffein stimulates the medullary centers, causing increased respiration and rise of blood-pressure, due to stimulation of the vasomotor centers, but this is complicated by cardiac and vascular effects, and slowing of the heart from stimulation of the vagus center, which is also complicated by the direct, and indirect, cardiac actions. Obviously, the effects on the circulation are complex, and variable.

Wakefulness is one of the most frequently observed effects of caffein in those who are unaccustomed to its use, especially when it is taken shortly before bedtime, but it may promote sleep when sleeplessness is due to fatigue.

Caffein relieves certain forms of neuralgia, the etiology of which, and the mechanism of relief are obscure. It appears to enhance the antineuralgic actions of antipyretic drugs, such as antipyrin, with which it is sometimes administered.

Theobromin induces much less psychic stimulation than caffein, but it is convenient to consider them together because of the general similarity in most of their other actions.

The effect of caffein on cardiac muscle is important, but the muscular action is observed more conveniently

on skeletal muscle. Extremely small amounts of caffein, such as are utilized when solutions of 1:100,000 or weaker are employed in laboratory experiments, increase the force, efficiency and rapidity of contraction of voluntary muscle, but when more concentrated solutions are used, the muscle contracts less efficiently, less forcibly and more slowly, and finally goes into rigor.

Nearly all doses of caffein that produce any perceptible effect on the heart increase the rate, without increasing the force, and this effect with the stimulation of the vasomotor center results in at least a temporary rise of pressure, unless it is prevented by the antagonistic dilator action on the vessels themselves. Occasionally the force of the heart-beat is increased without any notable influence on the rate. The continued use of tea or coffee in large amounts gives rise to intermissions, extrasystoles or other forms of cardiac irregularity, which usually disappear when the beverage is discontinued or taken in greater moderation; but it is not certain that these cardiac irregularities are due exclusively to the caffein present in the tea and coffee, for indigestion may play a part in the symptoms.

German clinicians employ caffein in cardiac disease much as they use digitalis, but while these two drugs have a certain degree of synergistic action, the total effect is quite different.

The effects of caffein on the circulation are of importance with reference to its diuretic action. The vasoconstriction which at first affects the vessels of the splanchnic region, causing a rise of blood-pressure, also constricts the renal vessels, so that the secretion of urine may actually show a temporary diminution; but this renal vasoconstriction soon gives place to dilatation while the pressure in the general circulation remains high, thus securing the best circulatory conditions for diuresis. There are many persons in whom caffein and theobromin do not induce active diuresis.

Caffein and theobromin are absorbed fairly readily from the gastro-intestinal tract. Theobromin is relatively insoluble, but there is vastly more fluid in the gastro-intestinal tract than is required to dissolve the

largest therapeutic dose. When it is desired to inject these drugs subcutaneously it is necessary to use them in combination with an alkaline salt such as sodium salicylate or sodium benzoate, to produce soluble preparations.

Caffein is probably broken down in the organism to dimethylxanthin before it acts on the kidney, and it and theobromin are excreted partly as dimethylxanthin, and partly as uric acid, but they do not cause any important increase in the output of uric acid under ordinary conditions. A small amount of unchanged caffein may appear in the urine after the administration of very large doses.

It is a matter of common experience that a certain degree of habituation on the part of the central nervous system occurs toward caffein on continued use, but the heart becomes more susceptible if large amounts are taken daily.

Very few fatal cases of poisoning by caffein have been recorded, and in view of the enormous use of the beverages containing it we must suppose that it is not a dangerous drug so far as the immediate peril to life is concerned; but minor toxic symptoms, including nervousness, cardiac irregularities, sleeplessness, lassitude, ill humor and headache are common; these usually call for no other treatment than the discontinuance of the beverage which is causing the trouble.

THERAPEUTIC USES

Caffein is used therapeutically for its diuretic action, especially in dropsical conditions and in nephritis, and also in cardiac disease. Aside from its diuretic action it is not easy to suggest a logical basis for its use in cardiac disease.

Caffein is one of the best of respiratory stimulants, because the stimulation has little tendency to pass into depression even with large doses.

The antagonistic action of caffein to that of morphin and other narcotics is strikingly illustrated in a well-known laboratory experiment. If a cat or dog be given alcohol until completely anesthetized, and caffein be then injected subcutaneously, the animal

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will speedily regain consciousness and make coordinated voluntary movements, often rising to its feet, or at least, to a sitting position. If anesthetized with ether previous to the administration of the caffeine, it may regain consciousness and not pass under the anesthetic again, as it does with alcohol, owing to the slowness with which the alcohol is eliminated.

Caffeine has an equally important, though not so striking, effect in animals under the influence of morphine, and on theoretical grounds should be given in preference to atropine as a respiratory stimulant in the treatment of poisoning by morphine and other narcotics.

Caffeine in the form of tea or coffee is often useful for the relief of headache due to overexertion and nervousness.

DOSAGE

Caffeine and theobromine or the several combinations of these bases with other substances may be administered in doses of from 0.1 to 0.5 gm. (2 to 8 grains). Caffeine, the citrated caffeine and theobromine are preferably given enclosed in a capsule or cachet or in the form of dry powder to be washed down with a copious draught of cold water. The combinations of caffeine and of theobromine with sodium benzoate and sodium salicylate are readily soluble in water and are usually administered in the form of simple solutions.

The intravenous injection of caffeine is not without its dangers; under no circumstances should it be injected rapidly into the blood-stream. The following experiments illustrate the danger: A cat required 150 mg. ($2\frac{1}{2}$ grains) per kilogram of weight to cause death, when a dilute solution was injected very slowly, but in another experiment the heart was stopped at once by the *rapid* injection of as little as 5 mg. ($\frac{1}{12}$ grain) of caffeine per kilogram. It should be remembered that this dose corresponds to about 0.30 gm. (5 grains) of caffeine for a man, or less than is commonly taken habitually by many persons daily in the form of tea and coffee without perceptible effects. When one recalls what was said regarding the effect of even fairly dilute solutions of caffeine on skeletal

muscles.

muscle, he will appreciate the danger of rapid intravenous injections of even small amounts of caffein. If it is desired to inject the drug directly into the circulation, for which there is no apparent good reason in therapeutics, the dose should not exceed 0.20 gm. (3 grains), which should be dissolved in a fairly large amount of salt solution, and the injection should be made slowly, so that at least one minute should be consumed in the injection. It is not recommended that caffein be injected intravenously in therapeutic practice, however.

MATERIA MEDICA

Caffeina.—Caffein, U. S. P. Caffein is identical with thein, guaranin and methyl theobromin. Chemically it is trimethylxanthin. It is a feebly basic alkaloid usually obtained from the dried leaves of *Thea sinensis* or from the dried seeds of *Coffea arabica* and also found in a number of other plants. It occurs as white, silky, glistening needles or as a white crystalline powder, odorless and having a bitter taste. Caffein is soluble (1:70) in water and (1:50) in alcohol. For administration in the form of solution one of the more soluble preparations is usually preferred.

Caffeina Citrata.—Citric acid Caffein, U. S. P. A mixture of equal parts of caffein and citric acid. It is a white odorless powder having an acid and bitter taste and an acid reaction. It is soluble (1:25) in water and in alcohol, but is not at all suited for hypodermic administration. Because of its acid nature it is incompatible in solution with substances like potassium iodid, sodium salicylate, sodium benzoate and the several nitrites. For combination with salicylates and benzoates the alkaloid itself should be used or it may be prescribed in the form of:

Caffeinae Sodibenzoas.—Caffein Sodibenzoate, N. F. A mixture of equal parts of caffein and sodium benzoate. This product is freely soluble (1:2) in water and it, or the corresponding combination with sodium salicylate, is usually used for administration in solution either by mouth or hypodermically.

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Theobromina.—Theobromin, N. N. R. Chemically known as 3, 7-dimethylxanthin. A weak alkaloidal base closely related to caffein, that occurs in *Theobroma Cacao*, *Kola acuminata*, and several other plants. It occurs as a white crystalline powder, odorless and having a bitter taste. It is almost insoluble in water, but readily soluble in alcohol. Because of its comparative insolubility it is usually administered in soluble combination with sodium salicylate or sodium benzoate, preferably the former.

Theobrominae Sodium Salicylas.—Theobromin Sodium Salicylate, N. N. R. A double salt of theobromin sodium and sodium salicylate first recommended by Graham in 1887. The product contains approximately 50 per cent. of theobromin and occurs as a white powder, odorless and having a saline taste. Theobromin sodium salicylate is readily decomposed and therefore incompatible with acids, even carbon dioxid being sufficient to decompose it.

Physicians commonly object to using the beverages tea, coffee and cocoa, when the diuretic action of caffein and theobromin is desired, on the ground that too much water is thereby administered. The argument is not always well taken; every patient must have some water, and large doses of caffein and theobromin may be given with strong beverages without increasing the minimum of water, and absorption from the gastro-intestinal tract takes place promptly.

CHAPTER II.—DRUGS WHICH ACT ON THE CENTRAL NERVOUS SYSTEM (CONTINUED)

B. DEPRESSANTS

MORPHIN

Morphin is much the most important member of the group, but others have special fields of usefulness. Opium depends for its therapeutic value almost exclusively on the morphin which it contains, but the action of morphin in opium is modified to a certain extent by other constituents present, this probably being an advantage in some conditions and a disadvantage in others. Not enough is known about the actions of narcotin to enable us to state definitely how it modifies the actions of the morphin in opium, but it is probably of no importance in most cases when opium is used therapeutically, though its action may assume some significance when toxic doses of opium are taken.

Thebain acts on the spinal cord much like strychnin, but it and codein are present in opium in amounts too small to influence the action of the morphin appreciably.

Opium contains a caoutchouc-like substance and other colloidal matter which interfere with the absorption of the alkaloids, and thus prolong the local action on the intestine after the oral administration of opium. With this exception we may consider the actions of opium and morphin together, remembering, however, that with massive doses of opium the convulsant action of the other alkaloids is probably concerned.

The discovery of morphin by Sertürner of Hanover in 1805 has been characterized as the greatest dis-

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covery in the field of *materia medica* and toxicology of all times, and Kobert has called attention to the fact that all subsequent discoveries of alkaloids, or plant bases, since then have resulted from modified repetitions of the work of that apothecary. Until then it had not been supposed that plants might yield principles capable of combining with acids to form salts. To-day, however, the alkaloids constitute the most important group of plant principles in the *materia medica*, one reason being that many of them can be prepared in a high degree of purity.

About 1850, Pravaz, a French soldier and surgeon, invented the syringe which is still known by his name and which he used for injecting ferric chlorid into aneurysms; a little later Alexander Wood utilized the syringe for the subcutaneous injection of morphin.

Morphin is known to contain two hydroxyl groups, one being phenolic, or united to a benzene ring, and the other alcoholic, or united to a group such as occurs in alcohols. Substitution in one or both of these hydroxyl groups serves to modify the actions of morphin in various ways. Codein, or methyl morphin, differs chemically from morphin only by having a methyl group (CH_3) replacing the hydrogen of one of the hydroxyls; ethyl morphin hydrochlorid (dionin) has an ethyl group in one of the hydroxyls of morphin; and diacetyl morphin (heroin) differs from morphin by having two acetyl groups in the hydroxyls.

The number of substances which may be formed in this way is very large, but none of the others has attained any considerable degree of importance in therapeutics.

Apomorphin is also derived from morphin, and while it retains the narcotic action to some extent, the specific emetic action which it acquires places it in the group of emetics.

Morphin has a variety of actions which are severally of therapeutic or toxicologic importance, and since these different actions cannot be seen to advantage in a single species of animal the effects are necessarily studied on different species. For example,



morphin exerts a strychnin-like action on the spinal cord, which can be observed very conveniently in the frog, but this is masked in the higher mammals as a rule by the more pronounced actions on the cerebrum and respiratory center.

Witkowski observed that the depressant effects of large doses of morphin on the central nervous system of the frog were comparable to those resulting after the removal of successive portions of the brain beginning above and proceeding downward. These several effects of morphin are not separated sharply, but with appropriate doses they can be made out with some degree of clearness.

Following these actions on the higher parts of the central nervous system, the spinal cord is first depressed, and then rendered hyperexcitable so that the later condition is scarcely distinguishable from that induced by strychnin.

It is often said that man reacts specifically to morphin, but the character of the action is modified materially with the age and sex of the patient and with the size of the dose; thus van Swieten observed that different amounts of the same preparation exerted varying types of action, and he obtained stimulation with small doses, and depression with large. Children occasionally show tetanic convulsions after opium.

Binz gives the following graphic description of the action of moderate amounts of morphin on the higher centers in normal man:

After some minutes pleasant sensations are usually experienced; the brain seems to be relieved from the confines of the skull; glittering fantastic visions appear; one is indisposed to move; questions are answered with stammering; beautiful visions appear, but the beauty is short-lived, the eyelids grow heavy, the limbs lie motionless; every impulse sent out to them from the brain dies away; the whole body feels heavy as lead, and soon one sinks into deep sleep which is indistinguishable from the normal, if the dose is not too large. The respiration and heart-beat are slowed, one lies asleep but he can be aroused by a loud noise to a confused condition, but only by stronger stimuli can one be aroused completely.

This description applies to normal man; hence it does not include the most pronounced action which follows the therapeutic use of small or moderate doses of morphin which lessen or abolish the perception of pain.

This analgesic action is exerted on the centers concerned with the perception of pain, not in the peripheral mechanism, for the effect is no greater in the immediate region of a subcutaneous injection than it is elsewhere. The belief that morphin has a local analgesic action has resulted in a number of irrational methods of application, for example, urethral injections and other local applications.

Lead and opium wash forms a poultice-like mass which retains the heat of the body while macerating the tissue, and the lead is astringent. Little or none of the morphin in the opium can be absorbed into the skin in such a case, and it is probable that mucilage of acacia could be substituted for the tincture of opium with advantage.

A comparison of the analgesic value of morphin and of hydrated chloral is afforded by observing their effects on rabbits. If one animal receives a hypnotic dose of hydrated chloral, and another an analgesic dose of morphin, it may be observed that the first reacts to painful stimuli, but the second remains awake or can be aroused easily. Of course, a massive dose of hydrated chloral will prevent any perception of pain.

A further advantage which morphin has over hydrated chloral is that it does not depress the heart and vasomotor centers. It must be remembered, when one speaks of the central actions of morphin and the absence of peripheral effects, that the actions on the gastro-intestinal tract constitute an exception.

Morphin is not actively hypnotic in doses which leave the respiratory center unaffected, the action on that center occurring with doses just larger than the minimal analgesic, but sleep often follows the use of a small dose of morphin when wakefulness is due to pain, which the morphin relieves.

The effects of morphin on the medullary centers stand next in importance to those exerted on the cere-

brum, the respiratory center being depressed with smaller doses than are required to affect the other centers. On these two actions, the analgesic in the brain, and the respiratory in the medulla, depend the greatest therapeutic uses of morphin, for the relief of pain and for the control of cough.

Morphin depresses the respiratory center in such a way that carbon dioxid in the blood no longer increases the rate of respiration, but it does increase the depth of the individual respirations as much as it does in the normal animal. This depression results in lessening the cough reflex. It may be well to remember that while morphin lessens or prevents cough, it does not cure the condition of which the cough is a symptom and in some cases a necessary result, since it may be necessary to remove the exudate in the air passages.

The respiratory center shows a peculiar susceptibility to chloroform after morphin has depressed it, and when morphin is used before general anesthesia ether is to be preferred.

Small doses of morphin have little influence on the vagus center in man, but somewhat larger doses stimulate it, and with toxic doses it and all the higher centers are depressed.

Patients who suffer from cardiac lesions may show a greater response to vagus stimulation than normal man, and as little as 10 mg. ($\frac{1}{6}$ grain) of morphin has been followed by Cheyne-Stokes respiration in a man suffering with aortic insufficiency. We have here a chain of effects for which Cushny offers this explanation: The respiratory disturbances due to the morphin cause vagus stimulation with decreased heart-rate and disturbed circulation, which in turn causes Cheyne-Stokes respiration. Atropin abolishes the slowing of the heart-rate by paralyzing the vagus endings, and the Cheyne-Stokes respiration disappears with the improvement in the circulation.

Small doses of morphin cause dilatation of the cutaneous vessels through the action on the vasomotor centers, increasing the actions of diaphoretic drugs which may be administered with it. Dilatation of

the cutaneous vessels from any cause may cause erythema, and this sometimes follows the use of morphin or opium. While small doses cause this cutaneous dilatation, large doses have the opposite effect, the skin appearing pale because of the constriction of the peripheral vessels and dilatation of the splanchnic, due to vasomotor depression.

Macht showed that perfusion of the coronaries with morphin and other opium alkaloids induced dilatation, but the amounts to which the coronaries were subjected in his experiments were incomparably greater than those which can act on them when opium or morphin is used clinically. Furthermore, alkaloids leave the blood stream very rapidly, and hence any direct action on the arteries would be fleeting at most.

Morphin stimulates the centers in the medulla which are concerned with vomiting with varying degrees of intensity. Emesis may result even with moderate doses, or where the narcotic action is delayed after large doses in man. Vomiting cannot be induced during deep narcosis; hence this symptom is commonly absent in the late stages of morphin poisoning, while nausea, at least, is a more common symptom with moderate amounts. This emetic action of morphin is of some importance in connection with its use in strychnin poisoning, in which morphin is sometimes recommended.

The convulsant action of morphin is not usually seen in man because he succumbs to the narcotic action before the effect on the cord can be developed, but children occasionally show hyperexcitability, or even convulsions, after poisonous doses of opium. The convulsant action of codein is more pronounced than is that of morphin relatively to the narcotic effect. Toxic doses of opium probably contain enough narcotin to add materially to the convulsant action of the morphin present.

Therapeutic doses of morphin have little direct action on the heart except that they may depress the accelerator mechanism, permitting the vagus to exercise increased control over the heart-rate; the action is commonly utilized in therapeutics. The slowing

which follows morphin is not always necessarily attributable to this direct action, for it may follow the relief of pain and anxiety, and the resulting rest and sleep.

The nauseant action of morphin is accompanied by some increase in the secretion of the bronchial glands, which is probably due in part to the excretion of the drug by them.

The pupils are not acted on by morphin directly, the miosis which is seen in morphin poisoning being due to the central action; it appears to be analogous to the miosis which occurs during sleep. This is worthy of attention because it is sometimes stated that the degree of antagonism between morphin and scopolamin can be estimated by changes in the size of the pupil. The actions are so different that little importance should be attached to the state of the pupils when morphin and scopolamin are used together.

It is very well known that morphin and opium lessen or abolish peristalsis and relieve pain in the gastro-intestinal tract. In this we have an example of the local analgesic action of morphin, but this is an exception to the rule and it is not seen elsewhere. Even here morphin does not relieve all pain by its local action. It abolishes sensory impulses from the mucous surface of the stomach, but not from the serous.

The behavior of the movements of the stomach after morphin depends on the dose and mode of administration, the gastric movements being increased by small doses, and the pylorus caused to contract firmly by somewhat larger ones, administered in such a way that they enter the circulation with a minimum of local action, as with subcutaneous injection, the effect being due to vagus stimulation.

Many investigators have endeavored to explain the direct and indirect influence of morphin on the gastro-intestinal tract, but there is still much to be learned on the subject.

Morphin does not interfere directly with the secretion of urine, but in larger doses it causes the sphincter of the bladder to contract, preventing urina-

tion; hence it is often necessary to empty the bladder by means of a catheter during morphin poisoning.

Morphin is absorbed readily from the gastro-intestinal tract, and more rapidly after subcutaneous injection. Opium is used in the form of a pill when it is desired to retard absorption in order that the local action in the stomach and intestine may be prolonged, the colloidal matter delaying the absorption of the alkaloid.

Various explanations have been offered for the alleged greater action of opium than of an amount of morphin equal to that which it contains, but there is no satisfactory evidence that opium has any advantages over morphin except those just mentioned, which insure its increased local action.

Morphin is fixed in the liver of some animals in considerable amounts, and a small proportion may pass into the urine, though testimony on this subject is conflicting; the kidneys are probably negligible as excretory organs when one is seeking to hasten elimination during morphin poisoning.

It is of the first importance that morphin is excreted into the stomach after it has entered the circulation, but it is probable that this excretion is not very active after the first hour following the absorption of the drug into the circulation. It is sometimes stated that the excretion into this organ goes on for many hours, but it is probable that in such cases absorption has been prolonged.

It is surprising that we know so little about the rate of elimination of morphin by previously healthy man in view of its obvious importance in medicolegal cases. Since cumulation does not occur when morphin is taken several times daily by habitués, we must suppose that they, at least, are capable of destroying or excreting the drug fairly rapidly.

Morphin is not dangerous to the infant in the uterus, since it does not breathe through its lungs, but it is dangerous to administer it to the mother at such a time that it will be in the fetal circulation at the time of birth, as it depresses the respiratory center and may cause death. It is excreted in the

milk of the nursing mother, and may give rise to poisoning of the infant in that way.

The odoriferous principle of opium is excreted in the urine and may afford a clue in cases of suspected poisoning.

TOXICOLOGY

Few drugs have assumed greater toxicologic importance than opium and morphin, as the various tables of death by poisoning attest.

Habitués become careless and in many instances have taken overdoses with fatal effect. Morphin has been dispensed by error for quinin in many instances. The administration of soothing syrups to infants has been a prolific source of fatal poisoning. Morphin is a favorite method of suicide because of the painless death which it causes, but it is not so frequently used for the murder of adults as some of the more rapidly acting poisons, because the symptoms are apt to attract attention and treatment is so commonly successful. It is more commonly used for the murder of infants, however, and unfortunately, statistics on this score are probably of little value.

The importance of determining from what part of the cadaver any morphin was recovered may be illustrated by the following: A woman was found dead in a bath-tub of water. The person accused of her murder maintained that the dead woman had taken morphin as a preliminary to self-destruction by drowning. Morphin was found in the gastro-intestinal tract, but the chemist had not examined the duodenum and the ileum separately, and could give no information as to the source of that part of the recovered morphin. Fortunately, he recovered a notable amount from the gall-bladder, showing conclusively that it had been absorbed; it seemed so improbable that the woman could have carried out the purpose of drowning herself after the morphin she had taken had been absorbed into the circulation, that the accused was led to confess.

The fatal dose of morphin varies so widely with the circumstances attending its administration that it is

impossible to convey an accurate idea of the fatal dose in a single sentence.

It is often stated that infants are extraordinarily susceptible to all opiates, but several pediatricists have recently stated that very small children frequently take opium and morphin very well. It is not advisable for the general practitioner to disregard the almost universal testimony on this subject until we know more about the conditions under which opium and morphin may be given to infants with safety.

Reference to the pages of *THE JOURNAL* during the past few years will disclose the fact that many deaths have followed the administration of soothing-sirups to infants.

Morphin is oxidized readily into the harmless oxydimorphin. This change may even take place in old pills of morphin which contain acacia as an excipient; it may occur in solutions which are kept for some time; and it is induced almost instantly by potassium permanganate, which is therefore of great value in destroying any morphin with which it may be brought into contact in the stomach. This change also probably takes place slowly in the body when morphin has been taken.

The treatment of morphin poisoning demands the washing of the stomach at frequent intervals as long as the washings give any evidence of containing morphin; the bowels should be emptied by vigorous means in order to remove any of the poison that may have been excreted into the intestine or which reaches it from the stomach. The patient should be kept awake if this is possible without resorting to violent means.

Efforts should be directed toward sustaining the respiratory center; this may be so depressed that the respiration is insufficient long before death, and one should not wait for actual paralysis before beginning artificial respiration. Caffein is a valuable stimulant both for the respiratory centers and for the cerebrum. The free use of atropin is sometimes advised, but this is evidently a source of danger. It would be better not to use more than one, or possibly two, therapeutic doses of atropin, and if stimulation still be needed

resort should be had to caffein. Since the tonic contraction of the pylorus may prevent the passage of fluid into the intestine, antidotal drugs should not be administered by mouth, except such as are added to the water for washing the stomach.

The treatment of chronic morphinism cannot be detailed here, but it may be stated that other narcotics, such as belladonna, are usually substituted for the morphin until the painful stage of withdrawal has been passed. Relapses are common, but the treatment can be taken repeatedly, and an ultimate complete cure may be effected.

Morphin is decomposed at a temperature slightly above that at which it distils, and this is very near the temperature which obtains in the opium pipe. Hence the question has arisen whether the opium-smoker actually absorbs morphin or not; it seems probable that some morphin passes over with the smoke and, being inhaled, is absorbed.

THERAPEUTIC USES

The celebrated remark attributed to Sydenham, that few physicians would be so callous as to practice medicine without opium, suggests the variety of conditions in which the opiates are used.

Morphin stands first among drugs for the relief of pain. It often gives relief when used in doses which have hardly any other perceptible effect, but intense pain may require the use of the largest doses. Neuralgia affords one of the few examples of conditions in which other drugs are to be preferred to morphin as analgesics.

Alfred Pearce Gould states that in Middlesex Hospital Cancer Charity (London), where from 90 to 100 cancer patients are treated constantly, morphin is now used much less than formerly, and that in a ward having thirty-two patients, months may elapse between the administration of two doses of the drug, reliance being placed on aspirin and phenacetin for the relief of pain. He says that morphin often leads to more suffering than the disease.

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This suggests the inadvisability of resorting to morphin and opium unless they become absolutely necessary, in the early stages of malignant disease which tends to progress slowly and from which the patient may suffer for years.

Morphin often affords relief to patients suffering with cardiac disease, and while various suggestions have been offered in explanation of its action in such cases, we are unable to say on what actions the relief depends.

There are comparatively few conditions in which morphin is indicated as a simple hypnotic, since we now have a series of drugs better adapted for this purpose, but sleep may be afforded by relieving pain which prevented it.

Morphin is useful to prevent cough when this is not attended with free expectoration and is of sufficient frequency to prove distressing, or when it interferes with sleep. When bronchial secretion is free the cough is necessary to remove it, and interference with the cough at this time results in the accumulation of fluid in the air passages, making the patient's ultimate condition worse.

Morphin and opium are used as diaphoretics, especially in the form of Dover's powder, in which the dilatation of the skin vessels by morphin promotes the diaphoretic action of the ipecac. Morphin allays restlessness; and this is very commonly utilized in the treatment of inaccessible hemorrhage.

The vasodilator action of morphin is sometimes used in the treatment of eclampsia, in which no other drug is so valuable, if enough be given, according to H. Oliphant Nicholson. He employs doses of 30 to 45 mg. ($\frac{1}{2}$ to $\frac{3}{4}$ grain) and as many as four of such doses in a day. It is said that the dilator action then induces diuresis.

Opium acts locally to diminish intestinal peristalsis, and this action is utilized in a variety of conditions, many of which do not require enumeration. Opium in peritonitis serves the double purpose of relieving pain and restlessness and of immobilizing the intes-

tine. It is useful in checking the excessive peristalsis in diarrhea.

Morphin is frequently used previous to general anesthesia to allay the nervous apprehension of the patient and to secure sleep. It also acts synergetically to chloroform and ether, less of which is required for general anesthesia after morphin than without it. The synergistic action of chloroform and morphin on the respiratory center appears to be a source of danger in their combined use. The depression of the respiratory center prevents, to a certain extent, excessive respiration accompanying variations in the depth of anesthesia. Accidental death from too rapid administration of ether is not common, with dogs, at least, after morphin; in fact, it is sometimes impossible to kill dogs by the ordinary administration of ether when they have previously received large doses of morphin.

Codein is now largely prepared synthetically from morphin, and is obtained in a purer form than it was formerly. Codein and ethyl morphin hydrochlorid are much less active than morphin, which they resemble otherwise. Codein is said to be only about one-tenth to one-twentieth as active as morphin, and while this may be true so far as the narcotic action is concerned, it is not used therapeutically in doses twenty times as large as those of morphin.

Its analgesic action is so slight as to make it much less valuable than morphin, but it does dull pain to some extent, and the probable absence of euphoria, which leads to the habit with morphin, is a distinct advantage of codein. It is said to have an especial value for the relief of abdominal and pelvic pain.

The actions of ethyl morphin hydrochlorid on the central nervous system are very similar to those of codein, and in addition it is irritant to the mucous membrane of the conjunctiva, this action being utilized in the treatment of conjunctivitis, iritis and corneal opacity, but it sometimes causes acute edema of the conjunctiva from local vasodilatation.

Ethyl morphin hydrochlorid (dionin) has been exploited to some extent as an analgesic and sedative

but there is no satisfactory evidence that it is equal to morphin for these purposes.

Diacetyl-morphin (heroin) differs from morphin to a greater degree than codein and dionin. Diacetyl-morphin and its action in lessening cough have been known for many years, but it was not used therapeutically until Dreser investigated it in 1898, and stated that it decreased the reflex excitability of the respiratory center toward painful stimuli, such as those which induce cough, more than it does toward carbon dioxid, the normal stimulant of the center. He also stated that it slows the rate of respiration while the depth and force of the individual respirations are increased, and he suggested that the increased force of the respirations would be of value in the treatment of bronchitis, in which the air-passages are narrowed.

Dreser experimented with rabbits, but it has been shown that his results do not apply to the use of heroin on man, and Cushny has shown recently that heroin influences the respiration exactly as morphin does; it has, therefore, no evident advantage over the older drug in the treatment of cough.

Diacetyl-morphin is much more toxic than morphin and must be used in correspondingly smaller doses. It gives rise to the habit quite as readily as morphin does, and the habit is as difficult to break and fully as injurious.

Diacetyl-morphin is said to be less actively narcotic in proportion to its activity on the respiratory center, and it is also less actively analgesic than morphin; its use should be limited, therefore, to the relief of cough, if, indeed, it were not better to use morphin or codein in these cases also.

Indian cannabis is usually classified with the morphin group, but its action is feeble compared to that of opium, and its effects are so uncertain that it is probable that there is no condition in which opium or morphin does not deserve the preference.

Extract of Indian cannabis is said to be a constituent of the extensively advertised proprietary hypnotic Bromidia, and it is probable that the continued belief in the value of Indian cannabis as a hypnotic is due in no small measure to its exploitation in this preparation.

DOSAGE

Morphin sulphate is analgesic in doses of from 3 to 15 mg. ($\frac{1}{20}$ to $\frac{1}{4}$ grain), the smaller doses lessening or abolishing mild pain, (such as may interfere with sleep) and intense pain requiring the larger dose. Even this may require repetition before relief is afforded, but it is preferable to use an insufficient dose and repeat it in half an hour, rather than run the danger of giving too large a dose at once.

The dose used for the relief of cough varies widely, dependent on whether it is desired to lessen the frequency of a troublesome cough without interfering with its removal of the secretion, or to abolish a severe irritative "dry" cough, which interferes with sleep. The former will require from 1 to 2 mg. ($\frac{1}{60}$ to $\frac{1}{30}$ grain) and the latter will require somewhat larger doses and more frequent repetition. Eight mg. ($\frac{1}{8}$ grain) of morphin or 0.06 gm. (1 grain) of opium in the form of Dover's powder is used for its diaphoretic effect. A single dose taken on retiring is a popular treatment for "colds." When morphin is used just prior to general anesthesia, the dose is from 8 to 16 mg. ($\frac{1}{8}$ to $\frac{1}{4}$ grain), and when used some hours previously to secure sleep and allay apprehension, the larger dose will be required usually, or the smaller dose may be used and repeated when the effect begins to pass off.

The aim with all narcotic drugs should be to secure the desired action with the absolute minimum of the drug, and it is always best to give a small dose when there is any doubt concerning the amount which will be required and repeat it if necessary.

Codein and its salts are given in doses of 0.03 gm. ($\frac{1}{2}$ grain) or more, this dose corresponding to approximately 0.003 gm. ($\frac{1}{20}$ grain) of morphin. Its use can be long continued without much fear of giving rise to the habit.

Half the dose may be used and repeated with correspondingly greater frequency when desired.

The average dose of diacetyl-morphin, or heroin hydrochlorid, is 3 mg. ($\frac{1}{20}$ grain). Its use should not be long continued because of its extreme tendency to induce the habit.

MATERIA MEDICA

Morphin, an alkaloid obtained from opium, is the chief therapeutic constituent of the drug.

In medical literature the term "morphin" is habitually used indiscriminately for the alkaloid and its salts, but the prescriber should not write "morphin" when the sulphate, or other salt, is desired. Morphin and its salts occur in commerce as colorless or white crystals or as a crystalline powder, odorless, and having a bitter taste. The dose of the several products is comparable and from a practical point of view the only important difference to note is their solubility in water and in alcohol.

Morphin is official as:

Morphina.—Morphine, U. S. P.

Morphinae Hydrochloridum.—Morphine Hydrochloride, U. S. P.

Morphinae Sulphas.—Morphine Sulphate, U. S. P.

The solubility of the several constituents varies considerably and suggests the limitation to the possible uses.

	Water	Alcohol
Morphin is soluble in.....	3,330 parts	168 parts
Morphin hydrochlorid is soluble in	17.2 parts	42 parts
Morphin sulphate is soluble in.....	15.3 parts	465 parts

Several additional salts of morphin have been used, more notably the acetate, but because of its unstable character and the fact that the liberated alkaloid is only slightly soluble in water, this salt has fallen into disuse.

Apomorphinae Hydrochloridum. — Apomorphin Hydrochloride, U. S. P. (See under Emetics.)

Opium.—Opium, U. S. P. The concrete milky exudation of *Papaver somniferum*. In medicine it is usually used in the form of:

Opii Pulvis.—Powdered Opium, U. S. P. The forthcoming pharmacopeia will require that powdered opium contain 10 per cent. of morphin, or about 20 per cent. less than that required by the U. S. P. VIII.

Extractum Opii.—Extract of Opium, U. S. P. A powdered extract which when assayed by the official

process should yield 20 per cent. of crystallized morphin. For practical purposes this preparation has little or no advantage over the powdered opium and its use should be discouraged.

Tinctura Opii.—Tincture of Opium, U. S. P. Laudanum.

Tinctura Opii Deodorati.—Tincture of Deodorized Opium, U. S. P.

The forthcoming pharmacopeia will require that tincture of opium and the deodorized tincture represent 10 W/V per cent. of the powdered drug, as the U. S. P. VIII does, but since powdered opium will contain only 10 per cent. of morphin, the tinctures will contain only 1 per cent. of morphin.

The deodorized tincture of opium is made by removing the volatile oil and its resinous constituents from the aqueous solution by means of purified petroleum benzin and adding alcohol to the filtered solution. The two preparations are otherwise comparable and have practically the same uses.

Tinctura Opii Camphorata.—Camphorated Tincture of Opium, U. S. P. This preparation, popularly known as paregoric, represents powdered opium (0.4 gm.), benzoic acid (0.4 gm.), camphor (0.4 gm.), oil of anise (0.4 c.c.) and glycerol (4 c.c.) in diluted alcohol (to make 100 c.c.). This mixture is widely used and abused, and its promiscuous administration to children has been the cause of more harm than good.

Pulvis Ipecacuanhae et Opii.—Powder of Ipecac and Opium, U. S. P. Dover's powder consists of a mixture of ipecac (10 gm.), powdered opium (10 gm.) and sugar of milk (80 gm.).

Codein or methyl-morphin is official in several forms, and as with morphin, the word "codein" is applied in medical literature to the alkaloid and its salts. The official forms are:

Codeina.—Codein, U. S. P.

Codeinae Phosphas.—Codein Phosphate, U. S. P.

Codeinae Sulphas.—Codein Sulphate, U. S. P.

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These several forms of codein usually occur as crystalline powders, odorless and having a faintly bitter taste. The solubility in water and in alcohol is shown in the following table:

	Water	Alcohol
Codein is soluble in.....	120 parts	1.6 parts
Codein phosphate is soluble in....	2.25 parts	261. parts
Codein sulphate is soluble in.....	30. parts	1,035. parts

Ethyl-Morphinae Hydrochloridum.—Ethyl-Morphin Hydrochloride, N. N. R. This preparation, commonly known as dionin, usually occurs as a white crystalline powder, odorless and having only a slightly bitter taste. It is freely soluble (1:7) in water and (1:2) in alcohol.

Diacetyl-morphin (heroin) is generally used in the form of:

Diacetyl-Morphinae Hydrochloridum. — Diacetyl-Morphin Hydrochlorid, N. N. R. This preparation, commonly known as heroin hydrochlorid, is a salt of a base formed by the action of acetyl-anhydrid on water-free morphin. It occurs as a white crystalline powder, odorless and having a bitter taste. It is freely soluble (1:2) in water and in alcohol.

MORPHIN AND SCOPOLAMIN

Some years ago Schneiderlin, a surgeon connected with an institution for the insane, administered morphin and scopolamin to a patient in the institution for the purpose of diminishing the amount of general anesthetic necessary for a major surgical operation, and was surprised to find that he was able to remove a cancerous breast without administering chloroform or ether to induce general anesthesia.

After performing a small number of operations in which morphin and scopolamin were employed in this way, he suggested the use of the combination as a substitute for general anesthetics, or to render more than a few drops of the latter unnecessary for surgical operations.

Schneiderlin seems to have been under a misapprehension concerning the degree to which morphin and scopolamin are antagonistic, and to have supposed that they were synergistic only in their narcotic effects,

for he placed much stress on the importance of the antagonisms in their side actions. In truth, the antagonisms between morphin and scopolamin are of minor importance, but they have an extraordinary degree of synergistic action on the respiratory center, sometimes causing paralysis in minute doses of the combination.

The morphin-scopolamin narcosis was tried by many surgeons, but the fatalities following its use were so numerous that it was abandoned by the great majority of operators, but it has been exploited in a sensational manner both in Europe and in the United States as a preliminary to childbirth. Effective doses are not very dangerous to the mother, in the hands of those who have mastered the difficult technic of its use, but labor is frequently prolonged by its use and the death-rate among the new-born from asphyxia is certainly higher than with other methods in the hands of the general practitioner.

Under no circumstances should the single dose exceed 0.01 gm. ($\frac{1}{6}$ grain) of morphin and 0.5 mg. ($\frac{1}{125}$ grain) scopolamin, nor should this be repeated until the effects have passed (several hours). The combination is strongly contra-indicated outside of special institutions, and except in the hands of those who are trained in its use.

Morphin and scopolamin do not produce total insensibility to pain when used in doses which are safe, but they induce a peculiar condition—the so-called “twilight sleep”—in which everything is quickly forgotten, so that the mother has no recollection of anything that happened during labor.

An American manufacturer combines an extract of cactus, known as cactoid, with scopolamin (or hyoscin), claiming that the danger to the heart is overcome thereby; but it has been shown by several investigators that cactus and all its preparations are inert; hence such combination can have no advantage over the simpler one. Another manufacturer has sought to avoid the decomposition of scopolamin, to which the injurious action is attributed, by the addition of an alcohol, but this is of no practical advantage.

Various combinations of opium alkaloids under trade names, including Omnopon, Pantopium and Narcophin, have been introduced with the claim that they have all the advantages of morphin without the side actions, but independent observers have not found the expensive substitutes preferable to morphin.

ANTIPYRETICS AND ANALGESICS

The drugs of this group are classified conveniently under this heading, though they are seldom used therapeutically for the reduction of temperature alone. The discussion of their actions will be facilitated by a brief consideration of the regulation of body temperature in health and in fever.

There is no known anatomic center for the direct regulation of the body temperature, but there is certainly a coordinating mechanism, in addition to any local mechanism in the skin, whereby the temperature of the body is maintained both in health and in fever, and reference to this mechanism is made when the heat-regulating centers are mentioned.

The efficiency of the heat-regulating mechanism is shown by the fact that the production of heat may be increased 60 per cent. by taking food, or during severe exercise, without causing a rise in the temperature of the body.

Fever results from a change in the heat-regulating centers whereby they appear to economize the heat loss, so that while with any increase in the heat formation there is normally a compensating heat loss, during fever a slight increase in heat formation is attended with some increase in the loss, but not enough to prevent the temperature from rising to a given degree.

The centers do not lose control of the regulation, otherwise the temperature would continue to rise indefinitely, and in fact, during fever the centers are more sensitive to external changes in temperature and to the influence of drugs than normally. This increased sensitiveness may be looked on as the effect of stimulation of the centers by drugs or disease products. We may look on the antipyretic actions of the drugs of this group therefore, as depressant to

the heat-regulating centers, preventing them from maintaining the higher temperature, which then returns toward normal. This conception led to Schmiedeberg's classifying the antipyretics of this group as fever narcotics.

The antipyretic effect of quinin is due mainly to diminished heat production through its peripheral actions; the other antipyretics of the group lower the body temperature through their central action which increases the elimination of heat, but quinin also has some central action, and the other antipyretics lessen heat formation, so that their actions differ mainly in degree.

It seems probable that fever may have a protective value in infectious diseases, since it appears to favor the formation of antibodies, and it is no longer held that hyperpyrexia is responsible for many of the pathologic changes which are found at necropsy, and which were formerly attributed to the febrile temperature which was therefore considered so dangerous.

It was owing to this erroneous view that the antipyretics had an enormous vogue soon after their introduction, and for a time there was intense activity in the search for new and better drugs of this type.

QUININ

It is commonly stated that the therapeutic use of cinchona, from which quinin is prepared, began with the treatment of the Countess of Chinchon in Peru in 1638, during an attack of malaria. The Jesuits employed it in the treatment of malaria in Europe, and from the foregoing circumstances it was variously called, Chinchona bark, Cinchona, Peruvian bark, Countess' bark, Jesuits' bark or simply "the bark." At present nearly all of the quinin of commerce is obtained from cinchona cultivated in India and Java.

Quinin is a protoplasm poison and is capable of destroying various forms of animal and vegetable cells. While it exerts its toxic action on such a variety of structures, it is extraordinarily active in destroying certain low forms of life. In 1867 Binz observed that in weak solutions it killed the para-

mecium of hay infusion at once, and that in very dilute solutions (1:20,000) it exerted a markedly toxic action on them, though they were much more resistant to the action of other poisonous alkaloids such as morphin and strychnin. These observations led Binz to the conclusion that malaria is due to a parasite which quinin is capable of destroying readily. The correctness of this conclusion has been abundantly proved, of course.

Since the great value of quinin in the treatment of malaria depends on its destructive action on these micro-organisms, it may be worth while to present briefly the more important facts concerning their presence in the human body.

It is known that when the anopheles mosquito bites a patient suffering with malaria it takes the malarial fever organisms into its stomach with the blood which it draws; that this blood contains asexual forms and smaller numbers of others which take on the sexual form and after passing through a cycle in the body of the mosquito, are injected with the saliva into the body of a person whom the mosquito bites later. These organisms, known as sporozoites, enter the blood and attack red blood-corpuscles, assuming a form which then multiplies in the blood. The sporozoite undergoes segmentation, and with the breaking up of the red blood-corpuscles and discharge of the young parasites into the blood there occurs a paroxysm of malaria, that is, a chill followed by a hot stage, presumably due to the discharge of toxins into the blood-stream.

Quinin is most destructive to the young parasites at the time they are discharged into the blood-stream, and it is important that the administration be so timed as to secure a sufficient concentration in the blood during the time that sporulation occurs. Unfortunately, in addition to the forms which quinin destroys readily, there are others which are more resistant and which may survive to become sources of infection through the anopheles.

The testimony of eminent authorities appears to be contradictory concerning the capacity of quinin to prevent an oncoming paroxysm. Thus Osler states

that quinin has no power to prevent an oncoming paroxysm which attends segmentation; Ricketts states that quinin given some hours before the time of an expected paroxysm prevents segmentation and thus prevents the paroxysm. This is in accordance with the teaching prevalent in some malarial districts, and there can be little doubt that a large dose of quinin given four hours before the time of the expected paroxysm may prevent it, but it has no influence on a paroxysm which is just beginning.

The action of quinin on the blood and its capacity for causing hemoglobinuria have been the subject of much discussion. Quinin even in dilute solution is known to be capable of destroying both the red and the white cells of the blood in vitro. Hemoglobinuria has been observed frequently after the administration of quinin, which was therefore believed to be its cause. Hemoglobinuria may occur during malarial fever, however, without the administration of quinin, and the view now held by the most eminent authorities is that quinin is not the cause of the hemoglobinuria which sometimes follows its use in malaria.

It should be remembered that washed corpuscles behave differently toward various drugs in vitro from the way they behave when those drugs are injected directly into the blood-stream. For example, saponin destroys red blood-cells suspended in normal salt solution, but when a solution of saponin is injected into the blood-stream directly, the saponin is fixed by the cholesterin present in the blood and the red blood-cells escape injury. Binz states that 1 gm. (15 grains) of quinin hydrochlorate in 10 per cent. solution may be injected intravenously without causing injury to the blood. There would then be 1 part of quinin to about 5,000 parts of blood.

Very small amounts of quinin are capable of increasing the force of muscular contraction, but slightly larger amounts decrease the force and efficiency. This is of interest with regard to the action of quinin on the heart when large doses are given, and also with reference to the action on the uterus when quinin is used to increase the force of uterine contractions during labor. One can understand why it

should sometimes have the desired effect and why it should sometimes fail, owing to the difficulty of adjusting the dose with precision. It seems probable that the action of quinin will be useful when induced at such a period that a few powerful contractions will suffice to expel the fetus; but if labor is not nearly terminated the induction of a few powerful contractions may be followed by weaker ones, and labor may be prolonged through its depressant action. Fortunately, it does not cause spasm of the uterus as many of the oxytocics do.

Quinin is not used for its action on the musculature of the heart, but it is of toxicologic importance. It is also of interest to note that cinchonidin is more poisonous to the heart and much less actively destructive to the malarial fever parasites. Cinchonidin was formerly much cheaper than quinin, which it resembles closely in appearance and in physical properties, and for which it was often fraudulently sold.

Quinin lessens the action of enzymes and of oxidation and it causes a diminution in the amount of heat formed in the body through its lessening metabolism by its action on muscles and glands. With small doses this diminution in the amount of heat formed does not cause a fall in the body temperature during health, because the heat-regulating centers compensate for the change by causing a diminished loss of heat. During fever quinin acts as an antipyretic (aside from its specific action in malaria), partly through this diminution in heat production and partly by depressing the heat-regulating centers. It is said that this influence in diminishing metabolism is useful in certain fevers by preventing an undue loss of protein but it is probably of little value in this way.

Quinin has only a slight analgesic action, and this has a limited field of application.

TOXICOLOGY

The prolonged use of quinin may result in injury to various organs, but the heart, the central nervous system, the gastro-intestinal tract and the kidneys usually suffer most in such cases.

Moderate doses of quinin commonly cause ringing in the ears which lasts for some hours; large doses may cause partial or complete deafness, the effect being brief as a rule, but occasionally permanent.

Dizziness, headache, nausea and vomiting with disturbances of the circulation and respiration occasionally result, and it may cause cardiac failure; disturbances of vision are rare. Skin rashes are fairly frequent.

The average fatal dose of quinin probably lies between 8 and 15 gm. (120 and 240 grains), much depending on the rate of its absorption.

ABSORPTION AND EXCRETION

Even the least soluble of the salts of quinin are absorbed fairly readily from the gastro-intestinal tract. In order to secure the more rapid action the more soluble of its salts are sometimes recommended, but there are occasions when an insoluble salt is preferred because of its less pronounced bitterness. The use of the sulphate in the United States affords an example of the force of habit, the hydrochlorate, which is used almost exclusively in England, being much more soluble.

Thayer states that the rate of absorption and its total amount vary widely with the solubility of the salt used and the form in which it is administered, absorption being retarded when it is taken with the food. In view of the importance of securing the absorption of quinin at such a rate that the requisite amount will be present in the circulation at the time of segmentation of the parasites, it is unfortunate that our knowledge of the subject is so imperfect.⁴

It is probable that too much importance has been attached to the influence of the degree of solubility of the salts of quinin on their absorption, and too little attention to the selective capacity of the gastro-intestinal tract for absorbing them. The question is in need of further investigation. The utmost care should be exercised to secure aseptic conditions, when

⁴ Guinea-pigs were used in a recent study of the absorption of quinin, but this would appear to be an especially unfortunate choice of animal because rodents absorb certain vegetable poisons from the gastro-intestinal tract very slowly, and apparently not at all, in some cases.

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a salt of quinin is injected subcutaneously or intramuscularly, because of its destructive action on the tissues, which leads to abscess.

Quinin usually begins to appear in the urine shortly after its administration, and almost the entire amount may be excreted within two days. A part is excreted into the stomach after its subcutaneous injection.

THERAPEUTIC USES

The chief therapeutic uses of quinin have been suggested in the foregoing discussion, and the subject requires only brief consideration here.

Quinin finds its principal field of usefulness in the treatment of malaria, being one of the few directly curative agents in the materia medica.

It is a matter of little importance, so far as the action is concerned, which of the salts of quinin is used, provided the one chosen is so administered as to secure absorption at such a rate that the blood will contain the quinin some hours before and during segmentation, or when segmentation would occur if it were not prevented by the drug.

Cinchonidin has been used in some cases when an idiosyncrasy, real or fancied, prevented the use of quinin, but the slight antimalarial action and the toxicity of cinchonidin render it an unsatisfactory substitute for quinin.

Quinin is an active antipyretic, and while it may be of some value during protracted fevers, such as typhoid, by reason of its lessening metabolism, and thereby preventing excessive destruction of protein, it is not certain that this advantage will outweigh its disadvantages in such conditions.

Its use during labor has been mentioned. While it does not cause spasm of the uterus, it is not always successful in facilitating the expulsion of the fetus.

Small doses may be used as a bitter for improving the appetite and digestion; large doses have an opposite effect. It is sometimes used at the inception of a cold, but its value in such conditions is problematic. It is also used as an antipyretic and analgesic in influenza, but it is probably less effective than phenacetin

and salol. Opinions differ somewhat concerning its value in the treatment of blackwater fever.

It would not be profitable to attempt to discuss the innumerable conditions and diseases in which quinin has been used with reputed success; many of these cases merely serve to illustrate the tendency which the body shows to recover regardless of treatment—even when it is distinctly injurious—and it should hardly be necessary to state that such an active agent as quinin should never be used without having a definite action in view.

Quinin and urea hydrochlorid has been used as a local anesthetic in the same way as cocain.

Quinin is a prophylactic against malaria, and those who are exposed to the bite of the anopheles in malarial regions should take it regularly; but it is of course more sensible to screen houses and destroy mosquitoes than to trust to quinin alone.

DOSAGE

The widest diversity of opinion exists in regard to the dosage of quinin in the prophylaxis and treatment of malaria. Some authorities advise as much as 2.5 gm. (40 grains) daily during the active treatment, and smaller amounts at stated intervals afterward.

A dose of 0.6 gm. (10 grains) of a salt of quinin administered about four hours before the time of an expected paroxysm, and this dose repeated in two hours, will suffice to prevent segmentation and the paroxysm in many cases. When the paroxysm is prevented the administration of quinin should be continued for several weeks. Some advise the administration of doses of 0.3 gm. (5 grains) three times daily for one or two months; others prefer the administration of somewhat larger doses on those days when the paroxysms would fall had they continued, and none on the other days. It seems more logical, however, to use the drug every day. It is especially unfortunate that these questions of dosage have not been determined conclusively, for the continued administration of quinin in large amounts is certainly capable of causing harm in many cases, but the dan-

ger of moderate doses for two months is far less than that of an attack of malaria.

The prophylactic dose of quinin is probably 0.6 gm. (10 grains) daily, preferably taken in two parts.

The tincture of cinchona, or the compound tincture, is generally preferred when the bitter effect is desired; the dose of either is 4 c.c. (1 fluidram) taken just before eating.

MATERIA MEDICA

Cinchona.—Cinchona, U. S. P. The dried barks of several species of cinchona are official as Cinchona, and Cinchona Rubra; these are required to contain not less than 5 per cent. of the typical cinchona alkaloids. Powdered cinchona was used largely at one time, but it has been almost completely supplanted by quinin.

Tinctura Cinchonae.—Tincture of Cinchona, U. S. P. One hundred c.c. of the tincture represents 20 gm. of cinchona in a mixture of alcohol, water and glycerin.

Tinctura Cinchonae Composita.—Compound Tincture of Cinchona, U. S. P. This preparation, commonly called Huxham's tincture, is made from the red cinchona, with bitter orange and serpentaria as aromatics. The menstruum is like that of the simple tincture of cinchona.

Quinina.—Quinin, U. S. P. An alkaloid obtained from the bark of various species of cinchona. Quinin is a white flaky or microcrystalline powder, odorless and having a very bitter taste. It is slightly efflorescent in dry air and only very slightly soluble (1:1,750) in water but very soluble (1:0.6) in alcohol. Combined with mild alkalies like sodium bicarbonate to retard the development of bitter taste in the mouth, quinin alkaloid is perhaps as satisfactory as any of its insoluble salts.

Quininae Bisulphas.—Quinin Bisulphate, U. S. P. The acid sulphate of quinin occurs as colorless, transparent or as whitish needle-shaped crystals, odorless and having a very bitter taste. Quinin bisulphate effloresces when exposed to air and turns yellow on exposure to light. It is freely soluble (1:8.5) in water and soluble (1:18) in alcohol.

Quininae Hydrochloridum.—Quinin Hydrochlorid, U. S. P. The hydrochlorid of quinin occurs as white, silky glistening needles, odorless and having a very bitter taste. It is slightly efflorescent in dry air, and is soluble (1:18) in water and very soluble (1:0.6) in alcohol.

Quininae Sulphas.—Quinin Sulphate, U. S. P. The sulphate of quinin occurs as white glistening crystals or prismatic needles, odorless and having a very bitter taste. It effloresces rapidly on exposure to dry air and is only slightly soluble (1:720) in water but soluble (1:86) in alcohol.

Quininae Tannas.—Quinin Tannate, U. S. P. The tannate of quinin occurs as an amorphous pale lemon-yellow odorless powder, without taste or at most slightly bitter. It is only slightly soluble (1:800) in water but soluble (1:3) in alcohol. Quinin tannate contains only from 30 to 35 per cent. of anhydrous quinin, is less than one-half the strength of other salts of quinin and must therefore be given in correspondingly larger doses.

Quininae et Ureae Hydrochloridum.—Quinin and Urea Hydrochlorid, N. N. R. A compound of quinin hydrochlorid and urea hydrochlorid which occurs as white, interlaced prismatic crystals, odorless and having a very bitter taste. It is freely soluble (1:1) in water, which makes it available for hypodermic use.

The comparative value and uses of the salts of quinin enumerated above are suggested by the following table showing the relative percentage of anhydrous quinin in each and also the relative solubility in water and in alcohol.

	Per Cent. of	One part soluble in	
	Anhydrous Quinin	water (parts)	alcohol (parts)
Quinin	85.5	1,750.	0.6
Quinin bisulphate...	59.5	8.5	16.
Quinin hydrobromid	76.6	40.	0.7
Quinin hydrochlorid	81.5	18.	0.6
Quinin salicylate....	69.9	77.	11.
Quinin sulphate.....	74.3	720.	86.
Quinin tannate.....	30.35	800.	3.
Quinin and urea hydrochlorid	60.	1.	

Quinin and the several salts of quinin may be administered in the form of pills, capsules, cachets, tablets, troches, solutions and mixtures, but the form in which the article is administered should be adapted to the particular salt of quinin used. The solid forms, like pills and capsules, are, of course, adapted to any of the salts of quinin, while solutions of sufficient strength to be active can be made only by the use of the acid salts. Mixtures, on the other hand, are preferably used for the administration of the more or less insoluble alkaloid and tannate. A syrup of glycyrrhiza made by mixing one part of fluidextract of glycyrrhiza with three parts of syrup makes a satisfactory vehicle for any of the slightly soluble salts of quinin. A syrup of yerba santa, which was formerly much used as a vehicle for quinin, is now but seldom employed because it does not compare in elegance or efficiency with the syrup of glycyrrhiza outlined above or a syrup of chocolate, such as is generally used at the soda-water fountain of drug-stores. The commercial form of sweet chocolate is an excellent vehicle for quinin, either in the form of the syrup suggested above or as a simple mixture of quinin tannate or quinin alkaloid with the chocolate in the form of pastilles or troches.

In administering a mixture of quinin it is advisable to direct that the mouth be rinsed with a dilute solution of a weak alkali like sodium bicarbonate, before and after taking the dose of quinin, so as to avoid the bitter taste of a trace of alkaloid which may dissolve in the mouth.

SUBSTITUTES

Among the substitutes which have been proposed for the non-proprietary preparations of quinin are:

Euquinin, which is quinin ethyl carbonate and is claimed to have the same action as quinin with the advantage of being tasteless owing to its insolubility in water and alkaline medium. It is, however, sparingly soluble in water and readily soluble in alcohol and in acid liquids generally, and in solution possesses the characteristic bitter taste of quinin.

Saloquinin is salicyl quinin, the salicylic acid ester of quinin. It is thought to have the advantage of combining the properties of quinin and of salicylic acid. It is practically insoluble in water but is soluble in acidulated water and moderately soluble in alcohol. Like euquinin, when held in the mouth for an appreciable length of time, it develops a distinct bitter taste and therefore cannot be said to be absolutely tasteless.

These complex salts probably have little or no advantage over quinin alkaloid and quinin tannate, which are much cheaper.

ACETANILID, ANTIPYRIN AND PHENACETIN GROUP

The introduction of the antipyretics and analgesics of this group affords one of the most interesting chapters of medical history. The high cost of quinin, which resulted in its adulteration, led to efforts to discover a method of preparing it synthetically, and in addition to the cost of the alkaloid, its bitter taste, and its relative insolubility, which interfered with its use by subcutaneous injection, served as a stimulus in the search for a substitute for it. While these efforts were unsuccessful so far as the immediate aims were concerned, they did lead to the discovery of numerous synthetic compounds, including the antipyretic analgesics which have come into use during the past thirty years. Curiously, the best drugs of this group were among the earliest discovered, and the exploitation of the newer members has been largely mercenary.

Quinolin was used as the starting-point in the search for synthetic quinin or a substitute, because it results from the decomposition of quinin, and it retains the antipyretic action of the parent substance, but it is too toxic for therapeutic use.

Kairin and thallin were among the first of the synthetic antipyretics; they soon dropped out of use because of their toxicity. Antipyrin was prepared in 1884 by Knorr, who used phenyl-hydrazin as the starting-point, and who supposed that antipyrin contained two quinolin rings. It is now known to be phenyl-dimethyl-pyrazolon.

Anilin was known, as far back as 1861, to have antipyretic actions, but its toxicity precluded its therapeutic use, and the attempt was therefore made to utilize its antipyretic action while reducing its toxicity by introducing various radicals into the molecule. Acetanilid, which results from the introduction of an acetic acid radical into the anilin molecule, was one of the earliest of these synthetic anilin derivatives, and it continues to be the cheapest and one of the best. Paramidophenol, which is closely related chemically to anilin and phenol, was found in the urine after the administration of one of the antipyretics, and this led to its use as a starting-point in the preparation of synthetic substitutes for the older members of the group. The introduction of an ethyl group into the paramidophenol forms phenetidin, and the introduction of an acetic acid radical into this forms acetphenetidin, or phenacetin, as it is commonly called.

The antipyretic and analgesic actions of the drugs of the acetanilid and phenacetin type result from certain compounds, such as paramidophenol, which are split off in the body from the parent drug. If they are split off too rapidly the action is too violent, and if they are split too slowly the action is too feeble; hence the therapeutic value of a member of this group depends on a gradual splitting of the drug in the body. Innumerable compounds may be formed by the introduction of other aromatic acid radicals in place of the acetic, or other alkyl groups in place of ethyl, but none of these has proved superior to acetanilid and phenacetin. Some are split very slowly and therefore have very little toxicity, but they are also less active therapeutically, and some are more active therapeutically, but are also more toxic.

Fraenkel says that no cheaper and better substitute for antipyrin and phenacetin can be prepared from the parent substances, and that it is purposeless to continue to multiply these. While we should continue to search for improved antipyretics and analgesics, such improvement can come only with development along wholly different lines.

The various members of the group have closely similar actions, but they show considerable quantitative differences in activity.

Their classification as fever narcotics indicates their depressant action on the higher parts of the brain, and in addition to their depression of the heat-regulating centers, it is probable that they cause an actual paralysis of certain paths concerned with the perception of pain, because even small doses are usually as effective as larger ones in relieving certain forms of neuralgia. They have a slight tendency to induce sleep, and this tendency becomes more pronounced when one remains quiet after relief from headache or other pain, but the mental faculties may remain alert when one exercises them after the relief of headache.

Large doses cause collapse, with disturbance of the respiration and circulation. The heart may become feeble and death may result from cardiac failure, but this is rare, and it never occurs after acetanilid, antipyrin or phenacetin, except when overdoses are taken by enfeebled patients, or excessive amounts by those suffering from minor illness.

Severe, but not fatal, collapse is not infrequently seen after moderate amounts of these members of the group which are decomposed more rapidly than the three members just mentioned. If such rapidly acting members of the group are used, it would be better to employ minimal doses and repeat these more frequently than with the more slowly acting ones, but there seems to be no reason for their continued use.

These drugs do depress the heart somewhat, but this action is overrated by manufacturers of nostrums who claim that their preparations lack this cardiac effect because it is overcome by the addition of caffeine or other supposedly antagonistic substance. Curiously, caffeine and the antipyretic analgesics of this group have a synergistic action on the heart; hence large doses of such compounds are, if anything, more dangerous than the drug which they are intended to displace.

The antipyretic analgesics produce cyanosis when large doses are used, or when the smaller doses are

used continuously, and since they were known to injure the heart to some extent, it was supposed that this injury sufficed to explain the cyanosis. We know that the cyanosis is usually due to the formation of methemoglobin by the products of decomposition of the antipyretics, and the more rapidly they are decomposed in the body, the greater is the action on the hemoglobin. The milder actions leave the corpuscles intact, but with the more violent action the corpuscles are broken down. This does not take place when the drugs are mixed with blood in a test-tube, because the drugs are not then decomposed.

Those antipyretics of this type which are devoid of the action on the blood are also therapeutically useless, because the paramidophenol, or analogous substance, which causes the formation of the methemoglobin is also responsible for the antipyretic action and only those which are decomposed too slowly to exert a pronounced antipyretic and analgesic action are devoid of the action on the blood.

The antipyretics cause dilatation of the vessels of the skin; this promotes sweating, which is useful in the reduction of temperature; in case this is excessive, atropin should be administered in small doses.

The antipyretics, like narcotics in general, lessen metabolism and therefore the production of heat, but this is of much less importance than their action on the heat-regulating centers, for, as previously stated, it is through their influence on the loss of heat that the temperature is regulated for the greater part.

ABSORPTION AND EXCRETION

Antipyrin is very soluble in water, while acetanilid and phenacetin are only slightly soluble, but all are absorbed fairly readily from the gastro-intestinal canal, and are nearly always administered by the mouth.

The rate of excretion appears to depend on the rate of decomposition to a certain extent, and none of the drug appears in the urine unchanged after the taking of moderate amounts of acetanilid, which is decomposed more rapidly than phenacetin.

When the urine of a patient who has taken one of these drugs is exposed to the air, it may assume a

dark color because of the oxidation of certain of the decomposition products.

THERAPEUTIC DOSES

The antipyretic analgesics are not used so frequently as they were formerly for the reduction of body temperature alone, but they are used in much the same conditions for the relief of pain, such as that occurring with influenza; for headache, which accompanies so many types of fever; and to allay nervousness, thereby securing rest and sleep which are essential for the patients' well-being and the want of which is so injurious to the heart and nervous system.

They are sometimes used for the reduction of fever, when this is excessively high, but even in such cases the benefit derived is probably due mainly to one or more of the actions just mentioned.

They are widely used for the relief of headache arising in the greatest variety of conditions. They sometimes afford prompt relief with small doses, and often fail even when large doses are used. In fact, if a small dose fails to relieve headache or neuralgia a large dose seldom proves efficacious.

The wide-spread use of these agents by the laity for the relief of all forms of headache and neuralgia and for pain which often attends menstruation should be discouraged because of the danger of their indiscriminate use, and especially because of the frequency with which overdoses are used in unsuitable cases. The patient who has once obtained relief through the use of a given drug supposes that subsequent failure can be explained only on the basis of his having taken an insufficient amount, with the result that he repeats the dose many times. There is also the danger of the formation of the habit, whenever the drug is used in chronic conditions attended with headache or neuralgia.

Antipyrin is applied locally in concentrated solution as a styptic in hemorrhage of the nose. The antipyretic analgesics have a more limited field of action than morphin, being of little value in pain due to inflammation, but they deserve the preference over

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opium and morphin in those conditions, such as neuralgia, which they do relieve.

They should be used with caution in debilitated patients in whom the danger of collapse is exceptionally great. Some persons show an idiosyncrasy toward them and exhibit rashes or exanthemas after even moderate doses.

DOSAGE

The average dose of acetanilid is 0.2 gm. (3 grains), but it is better to use an initial dose of 0.1 to 0.15 gm. ($1\frac{1}{2}$ to 2 grains) and repeat cautiously when necessary. Antipyrin is given in slightly larger amounts, the average dose being 0.25 gm. (4 grains), and phenacetin is used in somewhat larger doses than antipyrin, the full dose being 0.5 gm. (8 grains), but it is seldom necessary to give more than 0.3 gm. (5 grains) for the relief of neuralgia or headache. The latter dose may be repeated at intervals of three hours until several doses have been taken when necessary. All of the antipyretics are more effective in reducing the temperature if given during a natural remission, and the later in the course of the remission, the smaller the dose required for a given effect.

It is probable that there is little difference in the danger of the several antipyretics mentioned above in the doses given. There is no question, however, that phenacetin is the least dangerous in equal amounts, but since it is also the least active therapeutically, this does not constitute an advantage with the proper regulation of the dosage. Many of the older and some of the later posologic tables give doses of the antipyretic analgesics which can hardly be considered entirely safe. While such doses may be used in certain cases, they are not to be recommended for routine procedure.

MATERIA MEDICA

Acetanilidum.—Acetanilid, U. S. P. The mon-acetyl derivative of anilin, $C_6H_5NH(CH_3CO)$ is official in several of the foreign pharmacopeias as antifebrinum or antifebrin. It occurs as an odorless crystalline powder having a slightly burning taste.

Acetanilid is only slightly soluble (1:180) in water but freely soluble (1:2) in alcohol.

Acetphenetidinum.—Acetphenetidin, U. S. P. Official in practically all of the foreign pharmacopeias as phenacetinum or phenacetin. Chemically it is known as acetparaphenetidin, $C_6H_4(OC_2H_5)NHCH_3CO$. It occurs as white crystalline scales, or a crystalline powder, odorless and tasteless. It is only slightly soluble (1:925) in water but soluble (1:12) in alcohol. It differs from acetanilid in containing the ethoxyl group C_2H_5O .

Antipyrina.—Antipyrin, U. S. P. Official in some of the foreign pharmacopeias under its chemical name phenyldimethylpyrazolon $C_3HN_2O(CH_3)_2C_6H_5$. It occurs as a colorless, almost odorless crystalline powder or tabular crystals having a slightly bitter taste. It is very soluble (1:1) in water and in alcohol.

All of the substances mentioned above are incompatible with spirit of nitrous ether and with oxidizing or reducing agents generally. Antipyrin being very soluble is more readily affected than the other two substances and all of them are preferably administered alone either in the form of capsules, cachets, pills or tablets. Antipyrin, being soluble, can be administered in the form of solution, care being taken to avoid complex mixtures and particularly preparations of any kind containing tannic acid.

Proprietary Preparations and Mixtures

The Council on Pharmacy and Chemistry gave its attention soon after its organization to several of the more widely advertised mixtures which were then claimed to be synthetic preparations. These preparations were found to be simple mixtures of acetanilid, caffen and sodium bicarbonate or other alkalies, and usually contained small amounts of tartaric or citric acid. The mixtures cost about 2 or 3 cents an ounce and were commonly sold for a dollar an ounce at wholesale. Since the enactment of the food and drug law in 1906 the composition of some has been changed, acetphenetidin being used in place of acetanilid. This further emphasizes the fact that manufacturers of nos-

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trums are in business primarily for profit, with little or no consideration of the interests of the consumer or of the physician who is utilized as an advertising medium for the several preparations.

No one will deny that mixtures containing coal-tar analgesics relieve pain in many cases. Since they are all sold direct to the public, the danger resulting from self-medication is obvious, because it has been definitely shown that mixtures containing caffeine and one of the antipyretics requires a special caution in their use.

In addition to these pretended synthetics, which are unworthy of further consideration, there have been introduced innumerable synthetic preparations of the general type of phenacetin or acetanilid with some added advantage, but unfortunately such advantage is invariably offset by disadvantages. For example, when one of these preparations is less toxic it is also invariably less active therapeutically. It is unnecessary to discuss these substances in detail, for, as we wish to reiterate, there is none which deserves the preference over acetanilid, antipyrin and phenacetin.

HYDROCARBON NARCOTICS

The terms "soporific," "hypnotic" and "narcotic" are sometimes used without a clear understanding of their meaning. "Soporific" (from the Latin *sopor*, sleep) and "hypnotic" (from the Greek *ὑπνος*, sleep) may be considered as having an identical significance; they are applied to drugs that induce sleep closely simulating natural sleep. The term "narcotic," (from *νάρκη*, stupor) is applied to those drugs which in moderate doses produce a more profound depression of the higher centers than occurs in natural sleep.

The following will serve to distinguish between them: Moderate doses of hydrated chloral induce sleep, during which sudden noises are perceived and their character recognized, while the patient is awakened to a normal condition, showing that the centers concerned with the perception of sound are almost as active as normally. Larger doses of hydrated chloral induce narcosis, during which the loudest noises do not awaken the patient nor can evidences of conscious-

ness be elicited by any ordinary means, such as shaking or pinching, the perception of pain being abolished, of course.

The stage of hypnosis passes gradually into that of narcosis, and while there is no sharp distinction between them, we use the terms "soporific" and "hypnotic" for such drugs or doses as induce the lighter stage of sleep, and "narcotic" for those drugs or doses which abolish the perception of pain and induce profound depression of the higher centers.

The hydrocarbon narcotics may be subdivided for convenience of consideration into the following groups: alcohol, chloroform and ether; hydrated chloral and other hypnotics. They have very similar actions in general, differing mainly in the rapidity with which their actions are induced and their duration; hence it will be convenient to discuss the subject of narcosis briefly, even though many of the drugs of this group are never actually used therapeutically for their narcotic effects.

Many theories have been advanced to explain the action of narcotics, and while none of these is satisfactory, there is one which has gained acceptance more widely than the others. Hans Meyer and Overton advanced theories independently which are similar in many respects, and which are usually spoken of as the theory of Meyer and Overton. They believe that the narcotic activity of different agents is dependent on their relative solubility in lipoids (lecithin-albumin compounds) and in water or serum, and that this activity does not within wide limits depend on the solubility in water or serum alone.

Meyer determined the relative solubilities of various agents in water and fats, or lipoids, designating this relationship as the "coefficient of distribution." He found that those having a relatively great solubility in lipoids are more actively narcotic than those having a relatively greater solubility in water. He believes that chemically indifferent substances enter the cells of the central nervous system by reason of their solubility in the cell envelope, and that their narcotic activity then depends on their possessing molecular

groups which affect the internal relations of cell compounds.

The chemically indifferent narcotic compounds exert their actions on all forms of cells which they penetrate, but not all substances having a relatively high degree of solubility in lipoids are actively narcotic, benzene, for example, being nearly devoid of this action.

Baglioni has suggested that anesthesia results from the withdrawal of oxygen from certain compounds in the central nervous system, and it is well known that narcosis results when the inspired air is deprived of oxygen. Other theories do not require mention here.

ALCOHOL

There are two diametrically opposed theories which are frequently urged to account for the earlier actions of alcohol on the central nervous system. Binz believed that alcohol stimulates the central nervous system, while Schmiedeberg holds that the action is wholly depressant and that such increased functioning as follows the use of alcohol results from the abolition of inhibition on the centers which normally exercise control over those which then show apparent stimulation.

The weight of opinion is in favor of the view that alcohol stimulates certain parts of the nervous system, the stimulation being brief, usually lasting about half an hour. Jacobi found that the motor areas of the cortex became hyperexcitable and that smaller differences in weight could be appreciated after alcohol, while even the largest doses did not cause paralysis of the motor areas.

There is no clear evidence that alcohol increases the capacity for performing the highest type of mental work, such as clear judgment and the exercise of sound logic require, but the evidence is overwhelming that the capacity for such effort is distinctly lessened, though rapid association of ideas and such feats as rhyming may be facilitated. Such stimulation as alcohol induces is soon followed by depression. The effects of the stage of stimulation are so well known

that they do not require detailed discussion here. The flushed face, the flashing eye, the ready wit, the good humor are sufficiently familiar to all.

Large amounts of alcohol lead to narcosis, which will be discussed when chloroform and ether are considered.

The respiration is greatly accelerated during the stage of excitement, just as it is during excitement from other causes, but the therapeutic use of alcohol results in a slightly increased respiration even during sleep. This is frequently attributed to a direct action on the centers in the medulla, but it is not known whether the action is direct or a reflex from the peripheral irritation. At any rate, respiratory depression does not occur unless the dose is large.

The vessels of the skin dilate after moderate doses of alcohol, and this dilatation is sometimes accompanied by a constriction of the splanchnic vessels which is sufficient to increase the blood-pressure slightly; but the changes in blood-pressure are only slight unless large doses have been administered, in which case there is a marked vasodilatation and fall in the pressure. It is not profitable to enter into a discussion here of the seat of this action, because the question is still unsettled.

The vagus center and that concerned with the emesis are probably not affected directly.

The heart-rate is not changed after therapeutic doses of alcohol, though the contraction may be slightly stronger, and it has been suggested that this is due to the supplying of energy directly by the alcohol. This, however, does not seem to be a satisfactory explanation. The behavior of the blood-pressure is inconstant, and it is probably of less importance than is the distribution of the blood.

Alcohol acts on the muscles directly and indirectly through the central nervous system. The direct actions are exerted in opposite directions. The immediate effect on muscular effort is to diminish the efficiency of the individual contractions, and the remote, to delay the onset of fatigue. Under its influence the muscle contracts less perfectly from the

start but continues at this slightly lower level for a longer time, with the result that more work is performed before it becomes exhausted. It must be understood that this action is available only occasionally, for the habitual use of alcohol interferes with muscular efficiency, as it does with nearly all of the functions of the body.

The reason for the delay in the onset of fatigue when alcohol is applied to the muscle directly is that the alcohol is oxidized to carbon dioxide and water, which are immediately removed, while the oxidation furnishes muscular energy, and the fatigue products accumulate more slowly than normally.

This action is probably negligible when alcohol is taken by the mouth, and the central action is then responsible for the increased capacity for muscular effort. It does this by facilitating the excitation of the motor areas and by lessening the perception of fatigue. Alcohol may therefore prove useful in an emergency, when it becomes necessary to continue physical exertion beyond the time when excessive fatigue would demand rest. The factors involved in increased voluntary muscular effort would not affect the action of the heart, and it is difficult to explain its improving the cardiac action on the basis of any direct action, or of the lessened perception of fatigue; hence we must suppose that any improvement in the condition of the heart which it induces must be secondary to circulatory changes.

The association of parental alcoholism and degeneration or pathologic conditions in the offspring have long been recognized. It is known that epilepsy is more frequent in the offspring of alcoholics than of abstainers; a recent report, moreover, calls attention to the fact that alcoholic intoxication in the father at the time of impregnation may result in an epileptic child even when there is but the single indulgence in alcohol.

Alcohol is absorbed rapidly from the gastrointestinal canal and it also favors the absorption of other substances, probably through its mildly irritant action on the mucous membrane.

Alcohol is eliminated fairly rapidly when small amounts are taken, the habitual user burning it faster than the non-habituated. It has been found that only about 2 per cent. of a dose of 70 gm. ($2\frac{1}{2}$ ounces) escaped oxidation when taken during rest, in which extremely small amounts escaped from the lungs. Ten times as much may escape oxidation and be eliminated by the lungs when alcohol is taken during exercise.

Gastric digestion is not materially affected by moderate amounts of beer and wines of low alcoholic content, and they may even promote digestion; but brandy and whisky, containing about 50 per cent. of alcohol, interrupt digestion when they are taken in sufficient amount, and digestion is not resumed until the concentration of the alcohol is reduced sufficiently through absorption or dilution with the gastric contents.

Alcohol is antiseptic, absolute alcohol being much less active than that of 70 per cent. strength. This is probably explained by the fact that the stronger alcohol dehydrates the bacteria, increasing their resistance to its penetration.

The continued moderate use of beer and other beverages of low alcoholic content commonly results in a gain of weight, due mainly to an increase in fat. Alcohol is also capable of sparing protein in those who have become habituated to its use, but not in those who use it only occasionally, or for a short time.

The dilatation of the vessels of the skin causes a sensation of warmth, because the increased blood-supply increases its temperature. This leads to a greater loss of heat than normally, and the body temperature may actually fall, even while one feels warmer, because the increased heat loss is not compensated for by increased heat formation. For this reason, the practice of taking alcohol before going out in extremely cold weather is dangerous, and severe exposure has often proved fatal under such circumstances. It is more rational to take alcohol when one returns to a warm room after having suffered from

exposure to the cold, for then sensation of warmth acts as a stimulant, while the warmth of the room prevents further loss of heat.

The treatment of chronic alcoholism cannot be discussed here in detail. Attention has recently been called to the often-observed fact that those who are fond of alcohol are not usually fond of sugar, while those who like sugar care little for alcohol; and it has been suggested that chronic alcoholism results from a disturbance of physicochemical balance, which may be corrected by diminishing the supply of alcohol and increasing that of sugar in the diet.

Common experience shows that individuals differ widely in their response to alcohol. The average fatal dose for a non-habituated adult is probably the equivalent of about 100 to 150 c.c. (3 to 5 fluidounces) when taken in fairly concentrated form, such as brandy or whisky. The more dilute forms, such as wine and beer, are not correspondingly active, because excretion then more nearly keeps pace with absorption. On the other hand, the more concentrated alcoholic beverages are more irritant to the stomach, and cause protective emesis more commonly than the weaker ones.

The first stage of alcoholism may be disregarded here, as it does not usually call for therapeutic treatment and is of minor toxicologic interest, but severe acute alcoholism, while rarely fatal, is extremely common and often demands treatment.

The more common type of acute alcoholism seen in habitués is different in several essentials from that seen in the non-habituated, and will be discussed first.

The common drunkard usually falls asleep under the influence of alcohol and will so remain if undisturbed, but when awakened he is prone to show excitement and extreme pugnacity that is difficult to control. The practice prevailing in some of the metropolitan hospitals in dealing with such patients is as follows: The stomach is washed, not so much to remove alcohol, which has usually been absorbed, as to remove undigested food and relieve nausea and vomiting, and to secure the retention of medicine. A dose of mag-

nesium sulphate (half a pint or more of 10 per cent. solution) is then passed through the tube and allowed to remain in the stomach with the object of causing active purgation. This is followed by the administration of large doses of paraldehyd—three or four teaspoonfuls every half hour until excitement is controlled. This may seem contra-indicated in alcoholic intoxication, in view of the similarity of action of the two, but it is said to act extremely well in controlling the delirium of inebriates. Of course it is not used when deep narcosis results from the alcohol, which is rare in these cases.

When extremely muscular inebriates cannot be controlled sufficiently during the maniacal stage to permit of washing the stomach, a hypodermic injection of apomorphin, 0.008 gm. ($\frac{1}{8}$ grain), suffices to cause emesis and quickly reduce the patient to docility.

Severe alcoholic intoxication in the non-habituated usually causes more profound depression than in the habituated, and this may succeed the first stage gradually, or may develop suddenly, causing death within a few minutes. During the narcotic stage there is active dilatation of the vessels in the skin, the face becoming scarlet, but soon there is a great fall of blood-pressure, due to the dilatation of the splanchnic vessels, and the skin of the trunk and extremities becomes cool and clammy, the respiration becomes stertorous, the pulse feeble. Emesis may occur at any time before narcosis develops, owing to the gastric irritation. When profound narcosis begins emesis stops, but it may recur as the narcosis passes away. The urine and feces are often evacuated involuntarily; with the failure of respiration the skin becomes cyanotic, as in asphyxia from any cause. The odor of alcohol on the breath is characteristic.

Chronic inebriates may of course present the stage of profound narcosis when the amount of alcohol taken is excessive, but this is unusual. The patient generally recovers after sleeping a variable length of time, but Kobert states that recovery seldom takes place after coma lasting more than thirteen hours.

Death occurs rarely from rapid failure of the respiratory center, or from apoplexy; edema of the lungs may result in death after some days. Cardiac failure or apoplexy may cause sudden death after the patient is apparently on the road to recovery, or this may result after some days from pneumonia or encephalitis. The latter is of interest in view of the suggestion that the headache which commonly follows a drinking bout may be due to pressure of cerebrospinal fluid on the brain due to increased secretion resulting from alcohol.

When a patient is seen after taking a dangerous dose of alcohol, the stomach should be emptied by the stomach-tube as promptly as possible, but, as previously suggested, this does not serve to remove much of the alcohol unless it is done immediately after the administration of the alcohol. If a dangerous amount of alcohol has been swallowed, the further treatment must be largely symptomatic—cold applications to the head, and warm applications to other parts of the body to prevent cooling. It has been suggested that venesection might be considered, but that would seem to be a council of desperation. It would seem to be more logical to inject as much as a liter (1 quart) of 2 per cent. solution of sodium sulphate intravenously in desperate cases, in order to dilute the alcohol which continues to circulate in the blood, and possibly to hasten elimination, though little benefit is to be expected probably.

Caffein is antagonistic to moderate amounts of alcohol, but its value in excessive depression is problematic. It should be administered intramuscularly (not intravenously) with caution and stopped if it fails to cause prompt, even though slight, improvement. Artificial respiration will be required if respiratory failure threatens.

Should the more threatening symptoms subside, the physician will be called on to treat the gastric disturbances and the headache which follow the narcotic stage. These demand the usual gastric sedatives, and caffein and potassium bromid for the headaches.

The following may be found of advantage in such cases:

Bismuth subnitrate.....10 gm. or $2\frac{1}{2}$ drams.

Make five powders and give one every three hours until all are taken.

The addition of an alkali is preferred by some and may be directed as follows:

Bismuth subnitrate.....10 gm. or $2\frac{1}{2}$ drams.

Sodium bicarbonate..... 5 gm. or $1\frac{1}{4}$ drams.

Mix and divide into five powders. Give one three times a day.

For the more aggravated case of alcoholic gastritis a moderate dose of cocain may be found advantageous.

Cocain hydrochlorid..... 0.05 gm. or 1 grain

Bismuth subnitrate..... 10.00 gm. or $2\frac{1}{2}$ drams

Syrup 20.00 c.c. or 5 fluidrams

Water to make.....100.00 c.c. or 3 fluidounces

Mix and direct that one tablespoonful be given and the dose repeated in two hours if necessary.

Caffein may be administered with the bismuth or preferably separately in the form of capsules either as caffein, citrated caffein, or caffein sodiosalicylate, 0.3 gm. (5 grains) in each capsule.

Potassium or sodium bromid as a sedative is best administered in the form of simple aqueous solution, 2 gm. or 30 grains in about 20 c.c. of water. The bromids are usually borne best when administered with simple carbonated water.

The high tax on ethyl alcohol has led to the abuse of methyl alcohol, which should not be used internally or externally on the body. A great number of fatal cases of poisoning have resulted from its use, and it has even more frequently caused blindness.

It is often claimed by the manufacturers of wood alcohol that blindness following its use is due to impurities present, but the purest wood alcohol obtainable causes it, and this action is explained by the retention of methyl alcohol in the central nervous system and its slow oxidation to formic acid, which acts on the retina, causing degeneration.

100 DEPRESSANTS OF CENTRAL NERVOUS SYSTEM

THERAPEUTIC USES

Few drugs have been used more extensively than alcohol, and few continue to be the subject of more heated debate. Cabot remarked that there are two camps opposed to each other concerning the actions of alcohol. In the one, those who believe alcohol to be useful in therapeutics are unable to give more than vague impressions that patients improve with its use, or to state wherein the improvement is shown. On the other hand, the opponents of the use of alcohol usually cite old experiments on animals in which enormous amounts were used, or the results obtained with soldiers, typesetters and others who were undergoing feats of endurance. Cabot found the action of alcohol to be practically nil with respect to the blood-pressure in 1,105 measurements on forty-one patients suffering with typhoid fever; nor could he observe any constant effect after therapeutic doses of alcohol with respect to temperature, pulse-rate, respiration rate, appetite, sleep, delirium or renal or cutaneous secretion in 2,160 observations on 309 patients in a variety of conditions. Cabot does not deny, however, that alcohol may have well-defined uses as a vasodilator and hypnotic.

One reason for the diversity of opinion concerning the therapeutic value of alcohol is that it is often used for its psychic effects, to buoy up the spirits of the patient and engender hopefulness and courage—conditions which physicians impart to their patients in such variable degrees by their manner and self-confidence.

It is obvious that alcohol effects changes in the distribution of the blood. In order to do this it must increase the blood-supply to some regions of the body and diminish that to others, and it is hardly conceivable that such changes should not prove beneficial in some cases and harmful in others. The selection of those cases in which the changes will be desirable, while avoiding the use of alcohol in those in which it will prove deleterious, will tax the knowledge, experience and patience of the practitioner.

It is often stated that alcohol improves the circulation in shock. One eminent pharmacologist calls attention to the dilatation of the vessels of the skin and explains the improvement sometimes seen after its use when the heart is beating feebly, as due to the lessened resistance to the contraction of the heart which this dilatation affords, thereby permitting recuperation. Another equally eminent authority cites this dilatation of the vessels of the skin as evidence that the splanchnic vessels are simultaneously constricted, according to the usual physiologic rule of compensating action between the peripheral and splanchnic vessels, and states that the improvement in the heart results from the increased blood-pressure, which of course increases the resistance against which the heart must contract, but which also affords a better blood-supply to the heart itself.

Alcohol may cause increased resistance at one time and decreased resistance at another, and while it is impossible to foresee which will follow in a given case, improvement in the condition of the heart may follow a rise of pressure when this was previously low, or a fall in pressure provided it was not previously too low.

When the heart is suffering with the effort to contract against high aortic resistance, the effect of the changes in circulation induced by the administration of alcohol will depend on the relative changes in the coronary and in the general circulation. If the blood-supply to the heart is increased in greater proportion than the amount of extra work thrown on the heart by a rise in the blood-pressure, the increased nutrition of the heart will cause an improvement in its capacity for meeting the added resistance, and its condition will improve; if, on the other hand, the rise of blood-pressure imposes an additional amount of work on the heart out of proportion to the increase in the coronary circulation, then the heart will suffer further injury. Since it is often impossible to foresee the direction which the change in circulation will take, it is better to use a small dose of alcohol and increase this cautiously if careful study of the circulation shows improvement.

Cardiac failure—not simply the actual stoppage of the heart, but the failure to maintain an adequate circulation—is often dependent in part on faulty respiration, and the action of alcohol in improving the respiration may react on the circulation and institute a cycle of improvement. Any improvement in the respiration which alcohol induces is usually little more than incidental, and we have other and better stimulants for the respiratory center.

It is generally admitted that alcohol is a food, but its value as a food is the subject of much uncertainty. It is not an ideal food, and even under the most favorable conditions it is utilized at the expense of injury to the organism. It must therefore be decided in any case whether the possible good will probably outweigh the harm.

Alcohol in the form of wine affords a pleasant hypnotic for occasional use, but its well-known tendency to give rise to the habit forbids the routine use of this beverage.

Alcohol is often used for bathing the skin in fever, and for hardening the skin to prevent the formation of bedsores.

MATERIA MEDICA

Alcohol.—Alcohol, U. S. P. In European pharmacopeias this article is usually designated as Spiritus, and varies considerably in strength.

The official U. S. P. alcohol is a colorless volatile liquid obtained by the distillation of the fermented mash of grain or other suitable materials which contain sugar. It should contain about 94.4 per cent. by volume of absolute alcohol, C_2H_5OH , and 5.1 per cent. by volume of water. Alcohol has a characteristic odor and burning taste and is miscible in all proportions with water, ether or chloroform.

In pharmacy it is widely used as a solvent, diluent and preservative and many of the extractive preparations, including tinctures and fluidextracts, contain from 30 to 80 per cent. of alcohol. As a diluent or vehicle it is frequently used in the form of:

Elixir Aromaticum.—Aromatic Elixir, U. S. P. An aromatic and sweetened elixir containing about 25 per cent. of alcohol by volume.

The potable forms of alcohol include malt liquors, such as ale, beer and porter, which contain from 3 to 6 per cent. of alcohol. Wine usually contains from 7 to 20 per cent. or more of alcohol, and distilled spirits, such as spiritus frumenti and spiritus vini gallici, contain from 40 to 50 per cent. of alcohol. It should be remembered that all these beverages contain, in addition to alcohol, aromatic principles and extractives that may be toxic or physiologically active.

GENERAL ANESTHETICS

CHLOROFORM AND ETHER GROUP

Every one who attempts to administer a general anesthetic at this period should have had a course of training in this special branch of medicine. Inasmuch as the general practitioner is called on at times to assume charge of patients who have been anesthetized, however, even though he may not have administered the anesthetic, this discussion will include a consideration of the more salient points. In addition, the practitioner would do well to read a fairly comprehensive treatise on the subject, such as that of Hewitt.

It is remarkable that ether and nitrous oxid were known long before they came into use as general anesthetics. Ether was prepared by Valerius Cordus in 1540—three hundred years before its use in anesthesia. Humphrey Davy in 1805 observed that nitrous oxid relieved an aching tooth, and suggested the use of the gas in surgery, but the suggestion went unheeded. Nitrous oxid was first used in dentistry by Horace Wells of New Haven, in 1844. He attempted to give a public demonstration in the Harvard Medical School, but this proved a fiasco, subjecting him to ridicule, and later he killed himself.

"Ether parties" were popular about a century ago. Crawford W. Long, a physician of Georgia, observed that he and his companions sustained small hurts without feeling the pain while under the influence of ether; this led him to perform the first surgical operation during ether anesthesia in 1842. Long took little trouble to make the results of his experience widely known, and the first public operation under ether

was performed by Warren at the Massachusetts General Hospital, Oct. 17, 1846. William G. T. Morton, a pupil of Wells, having learned of the action of nitrous oxid, had sought aid in its preparation from a chemist named Jackson, who suggested the use of ether. Morton adopted the suggestion and vainly attempted to keep its identity a secret for personal gain, but he spent the remainder of his life in advocating and popularizing its use.

Flourens announced in 1847 that chloroform acts much like ether on the lower animals, and Simpson of Edinburgh used chloroform as a general anesthetic in the same year.

Ether and chloroform were both used with little skill at this time, and Snow published the first comprehensive work on the subject in 1858. Ethyl chlorid anesthesia was known about as early as that of ether, but it attracted little attention for fifty years. A few years ago an effort was made to popularize ethyl chlorid, which was claimed to stand between ether and nitrous oxid in relative safety. This is not the case, and the use of ethyl chlorid is now limited to special cases.

Chloroform was the safer anesthetic at first owing to the want of understanding of the actions of ether, and for many years a mixture of alcohol, chloroform and ether was popular. The use of ether has increased steadily, and at present it is employed to a far greater extent than chloroform for general anesthesia. Chloroform still has a distinct field of usefulness, however, and with the swing of the pendulum in favor of ether, it seems that certain disadvantages of the latter may be overlooked.

The administration of a general anesthetic is always attended with danger, and the physician realizes that he may be called on to defend his choice of anesthetic should it be his misfortune to have a patient succumb during its administration. It always appears easier to defend the choice of that which is sanctioned by common practice than that which is indicated by careful study of all the conditions present in any given case, when such conditions happen to indicate the use of the less popular anesthetic; therefore physicians

tend to fall into the habit of selecting ether on all occasions regardless of whether it is best in a given case or not.

While statistics indicate pretty clearly that proportionally more deaths occur during the administration of chloroform than of ether, we are in need of a more comprehensive study with statistics of the ultimate dangers, including deaths which are indirectly attributable to the anesthetic. The "late chloroform deaths" have now become fairly well known, but many of the deaths from pneumonia which are due to the administration of ether are not reported as ether deaths. Ether is administered for minor surgical operations by professional anesthetists in many thousands of cases in which the patient, on regaining consciousness after the operation, passes from the anesthetist's care. If pneumonia develops several days later, the anesthetist may not so much as know that death resulted.

The following points are to be considered when choosing an anesthetic: sex and age (these are not usually very important, except where atheromatous arteries are to be expected); temperament; habits (alcoholism, etc.); general physique, obesity being unfavorable for chloroform and ether; respiratory and circulatory systems (difficulties present or anticipated in the respiration increase the risks of anesthesia). Morphinists are tolerant of chloroform and ether, but a dose of morphin administered to a morphinist just before the administration of an anesthetic makes this smoother. The mere bulk of the anesthetic is of importance on the battle-field, or where a sudden catastrophe demands the transportation of anesthetics for large numbers with insufficient facilities. In such cases nitrous oxid becomes impossible, and chloroform or ethyl chlorid is preferable. The time consumed in administering ether, especially in very hot weather and following battles, is also a great objection, and chloroform or ethyl chlorid is to be preferred on that account.

Probyn-Williams states that ether is the anesthetic of choice for patients between the ages of 6 and 60 years, chloroform being preferred for infants under 3, and a mixture of chloroform and ether for those

between the ages of 3 and 6. Chloroform is used for patients over 60, and it is used to induce anesthesia for those between 6 and 10 years, the anesthesia being continued with ether.

The actions on the central nervous system of chloroform, ether and ethyl chlorid resemble those of alcohol qualitatively in their essentials and need not be described in detail. It is of the first importance that these substances depress the higher parts of the brain and then the cord, while the medullary centers are affected to a much less extent.

The stage of excitement is important, but it is so well known that it does not require detailed discussion here; it is important where high blood-pressure is to be feared, and in such cases anesthesia is frequently induced with chloroform or nitrous oxid and continued with ether. At present it is customary in many institutions to induce anesthesia with nitrous oxid as a routine measure, and then proceed with ether.

With the administration of ether to man there is at first a sensation of suffocation and disturbance of the special senses, which are intensely disagreeable; chloroform is much less so. Excitement comes on after consciousness is disturbed. Sensation is commonly lost before the loss of motion in the voluntary muscles, and during this stage slight surgical operations, requiring but a minute or two, may be performed if muscular relaxation is not necessary, where there is no probability of severe injury which would give rise to injurious reflexes. With increasing depth of narcosis the reflexes are abolished, the winking reflex from touching the cornea being among the last to disappear, but not the very last.

During major surgical operations it is usually desirable to maintain that depth of anesthesia in which the corneal reflex is abolished, since this suffices to secure muscular relaxation while avoiding severe reflex injury to the central nervous system which occurs with insufficient depth of anesthesia. On the other hand, if this stage is exceeded materially, the respiratory and vasomotor centers suffer and the respiration stops. With chloroform the heart stops almost immediately

thereafter; with ether there is usually a slightly longer interval, during which the opportunity for resuscitation is greater than with chloroform.

The vasomotor and respiratory centers are not markedly depressed during a moderately prolonged anesthesia with ether, but the breathing is slower than normally, though it should be regular.

It is customary to discuss the action of the anesthetics on the respiratory and vasomotor centers separately, but the respiration and the circulation are so closely interdependent that it is impossible to injure one severely without injuring the other.

The respiration may be temporarily inhibited reflexly from the mucous membrane of the nose before the stage of deep anesthesia is reached, just as it may be in health by the inhalation of any irritant gas, but this does not occur during deep anesthesia. Irritation of the mucous membrane of the trachea may also give rise to persistent reflex inhibition of respiration, and this has caused death in some instances. When the respiration ceases early in the administration of anesthetics the respiratory passages should be examined carefully to insure that they are not the seat of obstruction or irritation from any cause. Of course, careful attention should be given to the air-passages before beginning the anesthesia, for it is obvious that interference with respiration in any way must prove dangerous. Imperfectly aerated blood causes a rise of blood-pressure, increasing the resistance against which the heart must contract, while it affords diminished nutrition to the heart, thus throwing an additional burden on it while it is enfeebled by lack of nutrition; this circulatory disturbance results in further injury to the respiratory center, establishing a vicious circle.

The circulation is subject to so many influences that it is difficult to determine in a given case the mechanism by which it may be disturbed. It is well known that ether, when administered properly for a moderate length of time, does not lower the blood-pressure.

The actions of anesthetics on the vasomotor centers have been the subject of much study, but there is a want of agreement on the subject, and we cannot deter-

mine whether the vasomotor center or the heart is responsible primarily for the fall which follows chloroform even with the greatest care. It seems probable that the heart and the vasomotor centers are but links in the chain which may be injured at either point.

With ether the blood-pressure may remain constant for several hours, but with the most careful administration of chloroform the pressure falls progressively, during which the heart evidently suffers.

The danger to the heart during the administration of chloroform is admitted by all, but this danger is variously explained. According to a view which has gained some acceptance, the heart becomes hyperexcitable and ventricular fibrillation results, with immediate failure of the circulation. It is maintained that overdosage has nothing to do with this effect, but on the contrary, that excessive caution has led to insufficient administration which favors hyperexcitability with the danger of fibrillation, whereas with the continuous administration of a sufficient amount of chloroform the ventricle is depressed so that hyperexcitability and the resulting fibrillation are impossible. The supporters of this view state that with a growing and excessive caution the number of deaths during the early part of chloroform anesthesia shows a marked increase.

It is maintained that anything which interferes with a smooth and uniform administration of chloroform increases the danger of ventricular fibrillation and that vagus inhibition is a source of danger only in so far as it interferes with a uniform condition of the circulation.

Every one admits the desirability of a smooth anesthesia, but it is not always attainable even with the greatest care.

The heart is subject to direct injury from the anesthetics in addition to the indirect through circulatory changes, chloroform being far more injurious directly than ether. The action of chloroform is dangerous at three different stages: soon after the inhalation is begun, and it may be before consciousness is lost; during the regular course of anesthesia; and one or several days after the anesthetization.

According to another view which has found wide acceptance, the source of danger to the heart early in the course of chloroform anesthesia is due to a combination of the direct action on the heart and the indirect through the vagus center as follows: When chloroform is carried to the heart in somewhat greater concentration than is desirable it causes the heart to become more susceptible to vagus control, and at the same time the vagus center is rendered hyperexcitable; at this time the irritation of the mucous membrane by the concentrated chloroform vapor sets up a strong reflex inhibition through the vagus center, causing the heart to stop. Vagus stimulation causes only a temporary stoppage of the normal heart, but when it pauses under the condition just cited the dilated chambers are filled with blood containing chloroform vapor in high concentration, and this vapor acting on the heart paralyzes it rapidly. It must be understood that this early danger to the heart may occur before the patient even loses consciousness, for one is prone to think that there is no danger so long as the reflexes are not abolished and the respiration and pulse are good. This danger is avoided by care in seeing that the chloroform is not inhaled in too great concentration and that the patient is not allowed to inhale too much of it when he begins suddenly to breathe deeply, as he may after a pause in the respiration.

The celebrated Hyderabad Commission overlooked this source of danger because they began their experiments by anesthetizing their dogs in a box where they were not easily observed. Even though they lost about 6 per cent. of their animals during the induction of anesthesia they were content to attribute all of these deaths to faulty technic or accident and did not investigate the cause further. In order to prove the real danger of concentrated vapor before consciousness is lost a later investigator succeeded in killing one-fourth of his dogs in this way intentionally.

Our discussion is not intended for the guidance of the expert anesthetist, who will rarely have any difficulty in avoiding overdosage, but the following experience illustrates the danger when chloroform is

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employed by those who are unskilled in its use: The medical students of a class who had previously used ether exclusively as the anesthetic in laboratory experiments were directed on one occasion to employ chloroform. Its nature was explained, and *extreme* caution was enjoined. Despite this caution too much chloroform was used with fatal results in nearly every one of the next series of experiments on dogs.

Chloroform causes a nearly constant fall in the blood-pressure, and the heart and respiration may fail rapidly at any stage of the operation, especially if the operation involves severe injury to nerve trunks with resulting reflex injury to the centers. Such injuries are more common with light anesthesia than with that stage where the corneal reflex is abolished.

The third stage of danger to the heart is attended with degeneration, which is not limited to the heart but involves the liver and other organs. While this degeneration is often found at necropsy in such cases, the cause of death is not known, for greater degeneration may occur from various other causes without causing death.

It has been shown that chloroform and ether may contain various impurities, and it has been maintained that traces of certain of these impurities add to the dangers of anesthesia. It is of course impossible to deny that impure anesthetics might be dangerous, but Hale has shown that pure chloroform is as toxic as that which has stood exposed to light for two years.

It has also been shown that ether which contains small amounts of acetaldehyd does not induce post-anesthetic glycosuria in dogs more readily than pure ether.

The diet appears to exert a far greater influence on the toxicity of chloroform, and probably of ether, than do mere traces of impurities, and it has been shown that a diet of carbohydrates previous to chloroform anesthesia greatly reduces the tendency of the latter to cause necrosis of the parenchymatous cells of the liver and kidneys.

Ether cannot cause sudden death in a manner analogous to that described, early before conscious-

ness is lost, but it may cause death during the operation, for ether is also directly injurious to the heart, though much less so than chloroform. The following laboratory experiment serves to illustrate the great difference in the toxicity of ether and chloroform for the heart. Three frogs' hearts are excised and placed one in Ringer's solution, another in Ringer's solution containing 0.25 per cent. of chloroform, and the third in Ringer's solution containing 2 per cent. of ether. The first heart continues to beat for an hour or more. The one subjected to the action of chloroform ceases to beat within a few seconds; if it be transferred at once to pure Ringer's solution it may possibly be made to beat again, but it is usually found to be permanently paralyzed. The third heart, which is subjected to the action of ether, will usually continue to beat for a few minutes and if transferred at once to pure Ringer's solution will resume regular beats.

This experiment serves to explain why the attempt to resuscitate patients when the respiration ceases after ether is successful more frequently than when the same accident occurs with chloroform. After the respiration ceases with ether the heart is usually capable of beating, whereas after the administration of chloroform the heart is usually so severely poisoned at the time the respiration ceases that it soon ceases to beat. Chloroform is said to be about 250 times as actively toxic to the heart as alcohol if compared in molecular proportions.

While so much stress is usually placed on the action of chloroform on the heart, Hewitt states that in practice the majority of chloroform deaths occurring during operations are due to intercurrent conditions which are often not recognized; these include asphyxial states leading to circulatory failure, swelling of the tissues surrounding the air-passages and interference with the free entrance of air, which may lead to circulatory failure in a susceptible patient.

The kidneys participate in the excretion of chloroform and ether, and frequently suffer injury, especially in the presence of a previous nephritis. Chloroform is much the more irritant, but so much more ether is required for anesthesia that it causes approximately as much damage to the kidney as chloroform.

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The liver may also suffer degeneration, as previously mentioned, and the existence of hepatitis is a strong contra-indication for chloroform.

Ether causes a more copious secretion of saliva and also of mucus in the bronchial passages than does chloroform, and the saliva may be aspirated during sleep and give rise to pneumonia. Atropin administered previous to the anesthetic prevents this excessive secretion of saliva and mucus. This also suggests the necessity for oral antisepsis prior to anesthesia.

It is sometimes stated by surgeons that pneumonia follows ether anesthesia only as the result of carelessness, or through too great cooling of the body, but this is not correct; pneumonia may follow an extremely brief and carefully conducted etherization.

Ether, being quite soluble in the saliva, may be swallowed in sufficient amount to cause irritation of the stomach and give rise to nausea and vomiting. It is for this reason that slight nausea and vomiting are more common after ether than after chloroform, but severe and dangerous vomiting is more common after chloroform. The cause of this is not known.

Ether and chloroform are absorbed readily from the mucous surfaces, the rate of absorption during inhalation being proportional to the partial pressure of the vapor in the alveolar air, since the body temperature may be regarded as constant.

It is unnecessary to enter into a discussion here of the concentration of the vapor in the air and in the venous and arterial blood at the time of inducing anesthesia and during its maintenance. However important they are for the anesthetist, they belong to the more advanced study of the subject such as one finds in special treatises.

Cushny found that about 90 per cent. of the chloroform administered was excreted in the expired air during anesthesia, that the exhalation of volatile substances from the lungs is exactly analogous to their evaporation from aqueous solutions, and that the amount of a given anesthetic thus eliminated in the expired air depends on its affinity for water to a much greater extent than on its volatility. This explains

why ether, which is more volatile than chloroform, but also more soluble in water, is retained in the blood more tenaciously.

The amount of ether present in the blood at the end of anesthesia is reduced to about one-half in from five to fifteen minutes, and at the end of two hours there is only about one-fortieth as much in the blood. Ether can be detected in the breath, however, for a day or longer after even a brief anesthetization.

Chloroform also disappears rapidly at first, and is reduced to one-fortieth the original amount in about seven hours, which is a seeming contradiction to what was said of the more rapid exhalation of ether, but the amount of chloroform present at the start was much less, and a small portion of the chloroform is capable of entering into a relatively stable combination with some constituent of the blood.

Buxton states that the administration of oxygen lessens the deleterious effects of chloroform on the different organs.

Ether is sometimes used as an active respiratory stimulant in emergencies, 30 or 40 minims being injected intramuscularly. The effects are sometimes striking, but of course the injections cannot be frequently repeated, and they are of service only in tiding over an emergency.

French surgeons have advised the use of large quantities of ether as an antiseptic in abdominal surgery, but it is difficult to see what special advantage it has for this purpose and certainly it is capable of causing serious injury.

The volatility of ether constitutes a serious objection to its use in extremely hot climates, for it is difficult to maintain smooth anesthesia with it in very hot weather. Its inflammability is less of an objection now that electric lights are so commonly in use.

THERAPEUTIC USES

The principal therapeutic uses of the anesthetics are too well known to require discussion, and unfortunately, we know far too little of the special indications for one or the other of these in a given case.

It is recognized of course that certain conditions serve as a contra-indication for one or the other of these, but we are frequently in the dark regarding other conditions which would undoubtedly serve as contra-indications were they known, for the deaths which occur on the operating-table would not occur if these contra-indications were known and the conditions recognized in those cases.

Ether causes more excitement than chloroform; hence it is contra-indicated where excitement with its attending high blood-pressure is dangerous, but this does not mean that ether cannot be used in such cases after anesthesia has been induced by chloroform or nitrous oxid. Chloroform does undoubtedly serve a most useful purpose in such cases.

Chloroform is certainly strongly contra-indicated where the operation is prolonged, because of the progressive injury to the heart. Ether is probably more dangerous where inflammation of the respiratory passages indicates danger of pneumonia.

MATERIA MEDICA

Aether.—Ether, U. S. P. A liquid composed of about 96 per cent. by weight of absolute ether or ethyl oxid, $(C_2H_5)_2O$, and about 4 per cent. of alcohol containing a little water. Ether occurs as a transparent colorless mobile liquid, having a characteristic odor and a burning and sweetish taste. It is soluble in about ten times its volume of water and miscible in all proportions with alcohol, chloroform, petroleum benzin, benzene, fixed and volatile oils. Ether boils at about 55.5 C. and is highly volatile and inflammable. Its vapor when mixed with air and ignited explodes violently.

Aethylis Chloridum.—Ethyl Chlorid, U. S. P. A haloid derivative, C_2H_5Cl , prepared by the action of hydrochloric acid gas on absolute ethyl alcohol. It occurs as a colorless, mobile, very volatile liquid, having a characteristic, rather agreeable odor and a sweetish, burning taste. Ethyl chlorid is slightly soluble in water and readily soluble in alcohol. It boils at a temperature of 12.5 to 13 C. and on account

of its extreme volatility should be preserved in hermetically sealed glass tubes and kept in a cool place remote from lights or fire. Because of the difficulty of handling it, it is now rarely used for general anesthesia.

Chloroformum.—Chloroform, U. S. P. A liquid consisting of from 99 to 99.4 per cent. by weight of absolute chloroform, CHCl_3 , and 0.6 to 1 per cent. of alcohol. It occurs as a heavy, clear, colorless mobile liquid of a characteristic odor, and a burning, sweetish taste. It is slightly soluble (1:200) in water but is miscible in all proportions with alcohol, ether and the fixed and volatile oils. Chloroform may deteriorate under the influence of light and air; hence that intended for anesthesia should be kept tightly stoppered and protected from light. The vapors should not be allowed to come in contact with an open flame because of the irritant action of the gas which is formed.

HYPNOTICS

We have no theory based on observed facts which is capable of explaining the chemical causes of sleep, but it seems probable that sleep is induced by certain products of metabolism which accumulate during waking. If we could determine just what these substances are and prepare them in a form suitable for therapeutic use we should probably have an ideal hypnotic. The claim is often made that the ideal hypnotic has been found, but such claims invariably prove unfounded, and we find that the new preparation has undesirable, and even dangerous, side actions.

Every hypnotic tends to require increasing doses, while the side actions do not diminish correspondingly; hence it is better to use different hypnotics when it is necessary to continue their use for some time.

Small doses of the hypnotics depress the psychic and some other centers in the great brain, while exerting little influence on other parts of the central nervous system. Larger doses should be avoided in therapeutics because they depress the vasomotor and the respiratory centers.

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Alcohol and opium were formerly our principal hypnotics, but these have been superseded largely by others which may be divided into three main groups as follows: (1) those which depend on halogens for their action; (2) those depending on alkyl groups, and (3) those in which an aldehyd group or ketone group determines the action.

Lauder Brunton has stated that the requirements for sleep are: (1) hindrance of blood-flow through the brain (this is not necessarily attended with a diminution of the amount of blood in the cerebral vessels at any given moment); (2) depression of the functional activity of the brain (it is a matter of common experience that mental activity prevents sleep).

A hypnotic must have a selective action on the brain, and one of the objects sought by investigators is the discovery of compounds having this selective action in the highest degree, with a minimum of action on the medullary centers and the heart. This has led to the introduction of many substances of greater or less value, which have been introduced in most cases with enthusiastic praise of their advantages and a disposition to minimize their disadvantages, and even to deny that they have any side actions worthy of mention. This method of exploitation has frequently resulted in the abuse of these newer hypnotics, and many deaths have resulted from overdoses of them, for it must be remembered that there is no such thing as an absolutely safe hypnotic, and that overdoses of most of them are about as dangerous as an overdose of hydrated chloral.

HALOGEN DERIVATIVES

Aldehyd, or acetaldehyd, CH_3CHO , has some slight hypnotic activity, but it is of no therapeutic value, because the hypnotic stage is preceded by excitement. By the introduction of three atoms of chlorin, forming chloral, CCl_3CHO , however, we obtain a useful hypnotic. Chloral is converted into hydrated chloral by the addition of a molecule of water, and this is the form in which chloral is commonly used.

Chloral was prepared by Liebig in 1831, and tested on animals in 1860, but it was not used therapeutically until 1869, when it was introduced into the *materia medica* by Liebreich. He assumed that, because it is decomposed in the presence of alkalies with the formation of chloroform, this reaction occurs in the blood and that the slowly formed chloroform induces sleep.

The blood is practically neutral in reaction, and even though hydrated chloral were decomposed with the formation of chloroform, the amount so formed from a therapeutic dose of chloral would be wholly inadequate to induce sleep during more than a very few minutes, if indeed it would cause sleep at all.

Mering showed that hydrated chloral is excreted in the urine as tri-chlor-ethyl alcohol in combination with glycuronic acid.

The actions of hydrated chloral resemble those of chloroform qualitatively, at least, quite closely, the chief differences in their behavior being due to differences in their rates of elimination from the body. It will be unnecessary to detail the actions of hydrated chloral on the higher parts of the brain, since this type of action was discussed when alcohol was under consideration.

In the absence of pain sleep may be induced by hydrated chloral with doses which exert but little action on the respiratory and vasomotor centers. From this sleep one may be aroused easily by noise, or by any stimulus which would arouse one from ordinary sleep. With larger doses the sleep is deeper, and the vasomotor and respiratory centers suffer depression, constituting, with the direct action on the heart, the principal source of danger with overdoses.

The respiration is diminished during sleep from any cause, and with therapeutic doses of hydrated chloral there is probably no greater depression of respiration than occurs in ordinary sleep; that is, there is probably no direct action on the center by the drug. Toxic doses, however, do depress the center directly, causing a slower rate with some increase in the depth of the individual respirations. Cushny has shown that the normal response of the respiratory

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center to carbon dioxid is not altered by therapeutic doses of hydrated chloral, while toxic doses prevent the increase in the rate by carbon dioxid but do not affect its action on the depth; hence the deeper respirations just mentioned in chloral poisoning.

The action of hydrated chloral on the heart and the vasomotor centers precludes its use as a general anesthetic in man, though it is frequently used for this purpose in laboratory experiments. While the blood-pressure falls greatly with toxic doses, it still responds to stimulation by carbon dioxid, and the asphyxial rise of blood-pressure usually occurs after the cessation of respiration. The action on the heart is similar to that of chloroform.

Hydrated chloral is irritant to the mucous membranes of the mouth and gastro-intestinal tract, and when it is administered in too great concentration it causes nausea and vomiting, or if it be administered by the rectum it is expelled. This indicates that the solution of the drug should be well diluted with water or some bland fluid before being administered.

It should be remembered that therapeutic doses of hydrated chloral are not analgesic, and that when pain is the cause of sleeplessness a suitable anodyne, such as morphin or antipyrin, is to be preferred.

Hydrated chloral is absorbed rapidly from the gastro-intestinal tract, and it may be given by the mouth or rectum, the dose being the same by either mode of administration. It is excreted in the urine in combination with glycuronic acid. The rate of excretion probably varies widely with the dose and the effect which it has on the blood-pressure. A cat may remain under the influence of a just non-fatal dose for as much as three or four days, while another will recover from a dose equally as large in one day, and dogs eliminate hypnotic doses of hydrated chloral in three or four hours. It is probable that the more prolonged action is attended with a profound fall of blood-pressure which interferes with renal excretion, while the shorter duration occurs where the circulatory disturbance is insufficient to prevent the prompt elimination of the drug.

The capacity of man for eliminating this drug appears to occupy a place between that of the cat and dog.

The repeated use of hydrated chloral tends to induce the habit, and where hypnotics are to be used for some time, occasional recourse should be had to other members of the group, such as veronal or trional, in order to avoid the too frequent use of one drug.

Acute poisoning with hydrated chloral is not so common when the drug is used alone, because physicians very commonly appreciate its limitations and use it with due caution, but it is a constituent of the proprietary Bromidia, which is commonly used with much less caution, and acute symptoms in such cases are not rare.

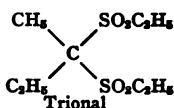
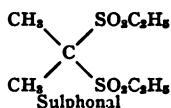
Absorption is so rapid that it is probable that little or no hydrated chloral remains in the gastro-intestinal tract when toxic symptoms are observed after the oral administration, but the stomach may be emptied when the patient is seen shortly after a poisonous dose has been taken. If the poison has entered the circulation, efforts should be directed toward its elimination, and proper symptomatic treatment should be instituted.

The respiratory and vasomotor centers, especially the former, are usually the seat of danger, and artificial respiration should be instituted when there is any sign of approaching paralysis. Schmiedeberg has recommended the use of coriamyrtin as a physiologic antidote to hydrated chloral, but it is a violent poison and probably has no advantage over the much safer caffeine, which stimulates both the respiratory and vasomotor centers. Active diuresis should be induced by the administration of hot drinks and in emergency, intravenous injection of warmed saline, as previously suggested in the treatment of strychnin poisoning, the object in both cases being exactly the same.

It is not sufficient to insure the safety of the respiratory center, for the more prolonged the elimination of the poison the greater is the opportunity for it to exert its toxic action on the heart. Hence the elimination should be hastened as much as possible.

SULPHONAL AND TRIONAL

These two substances are official as sulphon-methanum and sulphon-ethyl-methanum; chemically they resemble each other closely, differing only in that one of the methyl groups of sulphonal is replaced by an ethyl in trional. This is seen at a glance from the structural formulas:



Chemical compounds in general which have anesthetic or hypnotic actions dependent on the presence of ethyl groups are usually less depressant to the heart and the medullary centers than are those which depend on halogens for their action. Ether or ethyl-oxid has these disadvantages to a much less extent than chloroform, or tri-chlor-methane, and sulphonal and trional possess them to a less extent than hydrated chloral, or tri-chlor-aldehyd.

The discovery of the hypnotic actions of sulphonal was accidental. The substance had long been known when Baumann and Kast fed it to dogs during studies in metabolism and were impressed with its hypnotic action. This discovery led to the investigations of closely related products, but none of those discovered since has any great advantage over sulphonal, except that of greater solubility.

The actions of sulphonal and trional differ from those of hydrated chloral largely in their slighter effect on the heart and medullary centers, in their slighter solubility, slighter irritant action and their slower absorption with slower onset of action. They cause depression of the higher centers, inducing sleep in the absence of pain, with little disturbance of the respiration or circulation. Their toxicity is of importance almost exclusively with long-continued use, as very large single doses commonly cause only prolonged sleep, and slight disturbances.

Sulphonal and trional are relatively insoluble, so that they are given as powders or mixtures, and are slowly absorbed, the hypnotic action being usually

delayed for an hour in the case of trional and about two hours after sulphonah, which is even less soluble than trional. Occasionally the sleep may be delayed until the following day, or it may occur after the usual interval and drowsiness result on the following day with sleep at the usual hour some twenty-four hours after its administration.

The relative harmlessness of large doses of sulphonah is shown by the effects of a single dose of 100 gm. taken by a student. This was followed by unconsciousness in forty-five minutes. The temperature fell at first but later rose above normal. Sleep lasted five days; this was followed by exanthemas on the sixth day and complete recovery. In another case a dose of 30 gm. caused death from respiratory failure on the third day. Anemia increases the susceptibility to its action, and women are more susceptible than men. Such doses as these are never given in therapeutics and can be of importance only in case of accident or suicide.

The danger from the continued use of sulphonah is especially insidious, because one may take it in constant dosage for long periods without its occasioning any symptoms until these develop quite suddenly in severe form. About 60 per cent. of the cases in which symptoms of severe poisoning occur result fatally despite the most careful treatment.

The following illustrates the fact that long-continued immunity is no guarantee that this will continue:

A woman suffering from sleeplessness and hallucinations used daily doses of 1 to 1.5 gm. of sulphonah during three months, after which she became ill, vomiting greenish fluid, the urine was scanty and dark brown from hematoporphyrin; death was preceded by convulsions.

The urine should be examined frequently for hematoporphyrin in every case in which one of these drugs is used habitually. The appearance of hematoporphyrin in the urine indicates the destruction of the hemoglobin of the blood, and calls for the stoppage of administration and the administration of alkaline water in abundance to hasten the elimination of the poison. The treatment must be continued for several

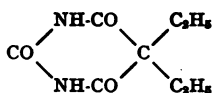
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weeks after severe symptoms develop. The actions of trional and tetronal are similar to those of sulphonal.

The earlier laboratory experiments indicated that tetronal was the most actively hypnotic, trional next, and sulphonal the least, but these results obtained on dogs do not apply to man, and trional has become the more popular, while tetronal has never acquired such popularity as the other two.

VERONAL

Veronal is related chemically and therapeutically to sulphonal and trional, its formula being;



Chemically, it is diethyl-barbituric acid, or diethyl malonyl urea. Its actions are elicited somewhat more quickly than are those of sulphonal and trional, and it is more active in equal amounts.

Soon after its introduction into therapeutics veronal was used in doses of 1 gm. and numerous deaths from it were reported. Experiments on animals indicate that veronal is slightly more active than hydrated chloral, equal doses of veronal causing an even greater depression, with fall of blood-pressure.

Numerous preparations which resemble sulphonal and veronal somewhat have been introduced as hypnotics, and while several of these have merit, the reader is referred to New and Nonofficial Remedies for a discussion of them.

ALDEHYDS

Acetaldehyd causes excitement before inducing sleep, as previously mentioned, but paraldehyd, a polymer of acetaldehyd, is more actively hypnotic without inducing excitement, and has less depressant action on the respiratory center. It is one of the safest of hypnotics, but it has an extremely unpleasant penetrating odor which pervades the room of the patient and which persists for more than a day; it has a persistent disagreeable taste. It has very little action on the heart even with large doses.

Several ketones are of pharmacologic interest, and a few compounds which depend on their ketone groups for their hypnotic action have been introduced into therapeutics; none are important. Acetone is actively hypnotic, and could be utilized therapeutically but for its irritant action on renal epithelium.

THERAPEUTIC USES

The actions of the hypnotics indicate their legitimate therapeutic uses, but caution is necessary regarding their use when sleeplessness is due to causes which can be removed. In other words, the hypnotics are in no sense curative, and should never be used when it is possible to induce sleep by removing or preventing that which interferes with it. Pain, worry, excitement and digestive disturbances are the common causes of sleeplessness, and these should be relieved or prevented by other means when possible. Pain should always be treated by analgesics rather than by hypnotics, of which large doses are required in the presence of pain, whereas small doses of analgesics suffice usually. The use of tea and coffee is a frequent cause of insomnia, and these should be stopped before resorting to hypnotics, of course.

Hydrated chloral is an antispasmodic, and is sometimes used to cause relaxation of the rigid uterine os during labor, and to abolish convulsions in tetanus; for this purpose large doses are required. It is used in combination with potassium bromid when sleeplessness is due to nervousness.

Hydrated chloral is contra-indicated in degeneration of the heart, and should be used cautiously in the presence of respiratory and circulatory disturbances. It is often recommended as an antidote to strychnin, but ether seems preferable in every way.

Sulphonal, trional and veronal are used as hypnotics in much the same conditions that hydrated chloral is, but minimal hypnotic doses have little action on the circulation and may be used when hydrated chloral is contra-indicated. These drugs should not be given continuously for prolonged periods, even when their use is attended with no visible signs of injury. They

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are also used as antispasmodics in epilepsy, hiccup, chorea and other conditions.

Paraldehyd may be used when hydrated chloral is contra-indicated by cardiac disease, or where a prompt action is necessary. It is also antispasmodic. Mention has been made of its usefulness in controlling alcoholic mania, and it is especially valuable in controlling mania during pneumonia and other diseases in which the heart is threatened with exhaustion and hydrated chloral is contra-indicated. Very large doses may be given in case of need without causing depression of the heart.

DOSAGE

Hydrated chloral is used in doses of 0.3 to 1.3 gm. (5 to 20 grains), but it is usually much better to employ it in the smaller doses in combination with twice as much potassium bromid where sleeplessness is due to nervous excitement; such a dose may require repetition in an hour, if sleep does not result. As an antispasmodic much larger doses may be required, but it is better to give the larger dose just mentioned and continue the smaller doses until relief is afforded, or until toxic symptoms indicate that the limit of therapeutic dosage has been approached.

The average dose of sulphonal or trional is usually stated as 1 gm. (15 grains), but 0.6 gm. (10 grains) often proves effective. The daily dose should not exceed 2 gm. (30 grains). The older tables gave the dose of veronal as 1 gm. (15 grains), but this is certainly too large for the average, and the dose should be from 0.3 to 1 gm. (5 to 15 grains).

The insoluble hypnotics should be given in the form of powders, which may be enclosed in capsules or suspended in hot milk, which is somewhat sedative, but which should be sipped and not drunk rapidly, as it forms an indigestible curd when taken in the latter way, whereas when sipped it is precipitated in flaky curds which are much more readily digested.

Hydrated chloral is best taken in a large amount of water or in warmed milk.

The dose of veronal sodium is about the same as that of veronal; it is more soluble and acts some-

what more rapidly. The aqueous solution has a bitter alkaline taste that is objected to by some patients. It should be given well diluted.

It is sometimes claimed that the greater solubility of the sodium salt insures its prompt elimination and prevents cumulative effects, but experiments on cats fail to substantiate the claim.

The average dose of paraldehyd is 2 c.c. (30 minims), best administered with cracked ice or in ice-water, on account of its disagreeable taste. It should not be long continued owing to the danger of the formation of the habit similar to that with alcohol. Much larger doses are usually required to control alcoholic mania, and from 10 to 15 c.c. (2 to 3 teaspoonfuls) may be given and repeated in half an hour.

A word of caution should be uttered here in regard to the use of Bromidia: This preparation is said to represent 15 grains of hydrated chloral, 15 grains of potassium bromid, $\frac{1}{8}$ grain of extract of cannabis indica and $\frac{1}{8}$ grain of extract of hyoscyamus in each teaspoonful of the preparation. It is obvious that if this formula is correct a teaspoonful of Bromidia contains four full therapeutic doses of hypnotics and narcotics. The ingredients are incompatible, because extract of Indian cannabis contains a resin not soluble in the menstruum employed. There is no excuse whatever for combining such a mixture of drugs when a simple hypnotic is required, and if an analgesic is necessary morphin or antipyrin should be used.

MATERIA MEDICA

Chloralum Hydratum.—Hydrated Chloral, U. S. P. This drug, popularly known as chloral hydrate, $\text{CCl}_3\text{CHO} + \text{H}_2\text{O}$, is the combination of trichloraldehyd or chloral, CCl_3CHO , with one molecule of water. It occurs as colorless, transparent crystals having an aromatic, penetrating odor and a bitter and caustic taste; it is slowly volatilized when exposed to air. It is very soluble in water, alcohol or ether. Hydrated chloral is incompatible with alkalies and alkali carbonates, which cause the formation of chloroform. A compound of chloral believed to be chloral alco-

holate sometimes separates out from mixtures containing hydrated chloral, an alkali, a bromid and alcohol. Hydrated chloral is best administered in simple aqueous solutions with or without the addition of a bromid. The bitter and caustic taste may be effectually masked by syrup and aromatics.

Sulphonmethanum.—Sulphonmethan, U. S. P. Diethylsulphonedimethylmethane, or sulphonal. The product of the oxidation of the mercaptol, obtained by the condensation of acetone with ethylmercaptan, is official in nearly all pharmacopeias and is generally prescribed in this country as sulphonal. It occurs as colorless, inodorous and nearly tasteless crystals or a crystalline powder; it is slightly soluble (1:360) in water and soluble (1:47) in alcohol. It is usually administered in the form of powder, preferably mixed with hot liquids such as weak tea, water or milk.

Sulphonethylmethanum.—Sulphonethylmethane, U. S. P. Diethylsulphonemethylethylmethane, or trional, is obtained by the condensation of methylethylketone with ethylmercaptan. It is official in many of the European pharmacopeias and is usually prescribed in this country as trional. It occurs as odorless, colorless, crystalline scales or a crystalline powder having a bitter taste in aqueous solution. It is slightly soluble (1:195) in water and freely soluble (1:10) in alcohol. Like sulphonal it is preferably administered in the form of a powder or mixed with hot liquids.

Veronalum.—Veronal, N. N. R. This substance is also known as diethyl barbituric acid, diethyl malonyl urea, and malo-urea. It is described chemically as 2,4,6, trioxy-5-diethyl pyrimidin, a ureid derived from diethylmalonic acid and urea. Veronal occurs as a white crystalline powder, odorless and having a faintly bitter taste. It is freely soluble (1:8) in alcohol and slightly soluble (1:500) in water. It may be administered in the form of powder or, like sulphonmethane and sulphonethylmethane, dissolved in hot liquids.

Sodii-Diaethyl Barbituras.—Sodium-Diethyl Barbiturate, U. S. P. This article, also known as medinal and veronal-sodium, is the mono-salt of diethyl-

barbituric acid or veronal. It occurs as a white crystalline powder, odorless and having a bitter alkaline taste. It is freely soluble (1:5) in water. Because of its solubility in water veronal sodium has been proposed for administration by rectal injection or hypodermically. Its use in this way has, however, as yet not been well established.

Paraldehydum.—Paraldehyd, U. S. P. Paraldehyd, $C_6H_{12}O_3$, is a polymer of acetaldehyd and occurs as a colorless transparent liquid having a strong characteristic odor and a burning and cooling taste. It is freely soluble (1:8) in water, and miscible in all proportions with alcohol. Paraldehyd is preferably administered with cracked ice or ice-water, but it is frequently objected to because of the odor which persists in the breath.

CHAPTER III.—LOCAL ANESTHETICS

COCAIN

Cocain is the only alkaloid of therapeutic importance obtained from coca. There are, however, other bases present in the leaf which probably add materially to its action, but which have not been studied.

The use of coca by the natives of Peru was mentioned by Pizarro in the sixteenth century, and at a very early date remarkable tales were told of the feats of physical endurance which the natives performed while using it. These stories were often considered as mere travelers' tales, but they have been amply verified, and the following interesting account of the endurance of coca-chewers is given by Lloyd of Cornell University:

We started across the Paramo, as the lofty summit of the Andes above the timber line is called. On this trip the dozen Indian porters who carried our cargoes all consumed coca unceasingly while on the march. After eating a simple breakfast of ground corn porridge, they would start with their heavy packs, weighing from 75 to 100 pounds, strapped to their backs. All day long they traveled at a rapid gait, over steep mountain spurs and across mucky swamps at an altitude that, to us, without any load whatever, was most exhausting. On these trips the Indians neither rested anywhere nor ate at noon, but incessantly sucked their wads of coca throughout the entire day.

The first investigation of cocain worth mentioning appears to have been made in 1860, when Woehler isolated cocain. The local anesthetic action of coca when chewed with ashes (as the natives use it) was observed a little later, and was shown to be due to cocain. Nothing came of these observations, however, until Koller, now of New York, introduced cocain into medical practice in 1884. For some years it was very expensive and its use was limited to ophthalmic practice. Its costliness, its toxicity and other disadvantages have served as a stimulus in the search

for substitutes, and many synthetic preparations have been introduced, but none of these has attained the popularity of cocain, though some have certain special fields of usefulness.

While cocain is used therapeutically almost exclusively as an anesthetic, its action on the central nervous system is of importance because of the frequency with which poisoning occurs through its abuse and through accident or overdosage.

Cocain stimulates the centers in the same general order in which they are depressed by morphin, but the motor areas, which are not depressed by morphin, are actively stimulated by cocain; this results in circus movements in some animals. The stimulation is followed by depression of the same areas, but the stimulation and depression are not at all uniform, so that one usually observes evidences of mixed stimulation and depression of the various centers during cocain poisoning.

Cocain causes a notable rise in the temperature, supposedly through its action on the heat-regulating mechanism.

The respiratory center in the medulla is stimulated, causing an increased rate, with little change in the depth at first. Later the stimulation gives place to depression, and with large doses the respiration becomes shallow, while the rate may be increased still further. If convulsions result, the respiration is arrested, and, as after strychnin convulsions, may fail to be reinstated, or there may be a gradual respiratory failure, with Cheyne-Stokes respiration and progressive slowing and diminished volume until death.

The vasomotor centers are stimulated by cocain, causing a great rise in blood-pressure, which may be so extreme as to demand treatment after large doses. It should be noted that this excessive rise in the blood-pressure is quite apart from the local vasoconstrictor actions which follow the local application of the drug, for in the latter case it is present in very much greater concentration than it can be after the absorption of non-fatal doses into the general circulation.

In discussing the peripheral actions of cocain we must distinguish between the local effects of relatively large amounts—that is, where the drug is in relatively high concentration in small areas—and the effects following the systemic application. The latter will be discussed first. Cocain stimulates the sympathetic nerve-endings after its systemic application, in which case the amount which comes in contact with the nerve-endings is insufficient to cause paralysis. The degree of the stimulation of the nerve-endings differs widely in different parts of the body. The accelerator nerve of the heart is stimulated prominently, causing an increase in the heart-rate; this tends to augment the rise of blood-pressure caused by stimulation of the vasomotor centers.

The sympathetic endings in the pupil are stimulated, causing dilatation of the pupil; this is also observed when the cocain is dropped into the eye.

The action of cocain on the sympathetic endings appears to render them more excitable to normal or other stimuli, even when the dose is insufficient to induce any visible effect alone. Thus if an amount of cocain equal to 0.3 mg. ($\frac{1}{200}$ grain) per kilogram of body weight be injected into the veins of a dog it will cause no rise in the blood-pressure, but if a dose of epinephrin that is too small to have any effect on the blood-pressure of a normal dog be injected intravenously immediately after the administration of the cocain, the blood-pressure rises sharply, because the vasoconstrictor endings are now more excitable than normally. The action of cocain is manifested on the pupil and probably elsewhere in the body in the same way. After the systemic administration of cocain the effects on the sympathetic endings elsewhere in the body are of minor importance, probably because the vasoconstrictor action, which results in a diminished supply of blood to the part, masks the action on the other sympathetic endings.

Cocain increases the capacity for muscular work through its lessening the sense of fatigue after its systemic application, but since it depresses the nerves with which it comes into contact in *sufficient concentration*,

cocain injected directly into the muscle to be tested diminishes its capacity for work.

The local application of cocain to mucous membranes causes constriction of the vessels, resulting in blanching, presenting a bloodless field for operations and causing stoppage of the secretion of the mucous glands through the interruption of the circulation.

This local vasoconstriction is useful in several ways. In addition to presenting a bloodless field, the interruption of the circulation delays the absorption of the cocain into the general circulation, thus intensifying and prolonging the local anesthetic action, and since the intensity of systemic action depends partly on the concentration in which the cocain enters the circulation, the slow absorption lessens this action while permitting the elimination of a part of the drug. Intense local vasoconstriction may follow the use of concentrated solutions, and the prolonged local action occasionally causes gangrene. This can be avoided by using dilute solutions, but their action is so slow and weak that the same object is attained better by using moderately dilute solutions of cocain with enough epinephrin to cause a sufficient degree of vasoconstriction.

When cocain is applied to mucous membranes or injected subcutaneously the nerve-endings are paralyzed, the sensory before the motor. If the solutions are applied to nerve-trunks these are also paralyzed, and here, too, the sensory fibers are paralyzed before the motor. The nerve-endings and trunks are not paralyzed when cocain is taken internally or injected intravenously, because it does not reach those structures in sufficient concentration. An apparent exception to this rule has been demonstrated for the serous surface of the intestine of the dog; pinching the intestine does not cause pain after the subcutaneous injection of a moderate dose of cocain.

The difference in the degree of concentration in which the drug reaches the nerve-endings of trunks after systemic and local application is appreciated when one remembers that the amount used for local application to an extremely small part of the body is

equal to that which can be injected safely into the entire body, and which is probably distributed through a large portion of it.

When cocain is applied to the tongue it abolishes the sense of taste for bitter substances more readily than those for sweet and sour, the taste for salt being unaffected. Yerba santa affects the sense of taste in the same way. The sense of smell is abolished by the local application of cocain to the nasal mucous membrane.

Cocain is absorbed rapidly from the gastro-intestinal tract and from the subcutaneous tissues when the local vasoconstriction has passed away, or if the solution injected is too dilute to cause this constriction of the vessels.

It is probably destroyed in the body in part, but a part is excreted in the urine unchanged, the elimination being slow after poisonous doses have been taken.

Acute fatal poisoning by cocain is comparatively rare, considering its wide-spread use. The fatal dose is probably about 1 gm (15 grains), either by mouth or subcutaneous injection, but a much smaller amount may be fatal when it is injected directly into the spinal canal, because of the facility with which it may ascend to the medulla and paralyze the respiratory center. Death is reported to have followed the injection of 0.02 gm. ($\frac{1}{2}$ grain) in this way in each of two cases.

Severe symptoms of poisoning may follow very much less than the average fatal dose.

The habitual use of cocain is common, and extreme measures have been adopted in some states, notably New York, in the effort to abolish the illegal traffic in the drug. The sudden withdrawal of cocain from one who has been accustomed to its use by subcutaneous injection causes such severe suffering and dangerous collapse that special provision must be made for the care of the habitués when stringent and effective laws are passed abolishing the sale of the drug except for legitimate therapeutic uses. Those who use it as a snuff are said to withstand the sudden withdrawal without serious consequences.

The treatment of cocain addiction requires special measures and does not demand discussion here. The treatment of acute cocain poisoning is similar in general to that of poisoning by other alkaloids—removal from the stomach, if possible, precipitation, elimination and administration of physiologic antagonists; there is no specific remedy for the drug when it has entered the circulation. Excessively high blood-pressure may require relief by means of the nitrates, 3 minims being inhaled from a handkerchief. Hydrated chloral or chloroform may be required to control the excitement and convulsions, but ether is probably preferable, because it is not so dangerously depressant, and its action can be controlled to accord with the different stages of cocain action better than hydrated chloral or chloroform.

Artificial respiration should be employed if there is any sign of respiratory failure.

Solutions of cocain are decomposed on prolonged boiling with the liberation of benzoic acid and methyl alcohol, but they may be sterilized with insignificant loss by boiling for a short time or by maintaining them at a temperature of 80 C. for an hour on each of two successive days. A solution recently prepared with proper caution with sterile salt solution is practically sterile. The solution decomposes on standing, and only freshly prepared solutions should be used.

THERAPEUTIC USES

The therapeutic uses of cocain depend almost exclusively on its anesthetic and astringent actions when applied to mucous surfaces, to painful ulcers, or when injected subcutaneously, and it is obvious that it is capable of affording relief in a wide range of conditions which it is unnecessary to discuss in detail.

When applied to mucous surfaces it causes anesthesia and intense blanching, due to vasoconstriction; hence it is applied to the conjunctiva, the nose, throat, urethra and other surfaces for the relief of pain, to facilitate examination or to allay congestion. It must be remembered that absorption takes place readily from any of these surfaces after the primary blanch-

ing, and sometimes immediately after the application. Death has followed the injection of a small amount of cocain into the urethra, though its injection into the bladder appears to be less dangerous, provided that dilute solutions are used.

The application of cocain in dilute solution or powder to the nasal mucous membrane relieves the congestion and facilitates the passage of instruments, but epinephrin is probably preferable. Cocain may be applied to ulcers when swallowing is painful, as in laryngeal tuberculosis, or it may be injected into the sheath of the laryngeal nerve, though this is not commonly advisable. Sometimes cocain is applied to itching piles and to the vulva, but it is better to employ phenol ointment, which does not give rise to a habit in such chronic conditions, for it must be remembered that absorption and systemic effects may follow the use of cocain in any of these conditions. The application of strong solutions to the gums and to carious teeth is said to be especially dangerous, and at most very small amounts of weak solutions should be used for that purpose.

Cocain is sometimes used to facilitate the swallowing of the stomach-tube, and to allay nausea of local origin in the stomach, but it is not advised for either of these purposes, because of the difficulty of applying enough of the solution to cause diminished sensation over such large surfaces without using toxic doses. It will be of very little use in allaying nausea of central origin, though it may diminish the stimulus from the stomach which acts on a hyperexcitable center.

Cocain is useful in securing a bloodless field in cutting operations on mucous membranes and operations of small area, but it is obviously unsuited for this purpose in major operations involving large areas. It is also especially effective in controlling capillary hemorrhage.

It is frequently used as a mydriatic because it induces insensibility to pain. The mydriasis is not so complete as with atropin, but the cocain is said to enhance the action of other mydriatic alkaloids, and a small amount of atropin may be used at the same time if desired.



Cocain does not cause paralysis of accommodation or the loss of reaction to light. The action is induced mainly through the local *stimulant* action on the sympathetic endings, but in part through the central action when absorption occurs. It is remarkable that atropin and cocain, which are so closely related chemically, should produce mydriasis through opposite kinds of action on different structures.

Cocain is sometimes injected intraspinally to produce insensibility to pain in the lower parts of the body, but while those who have become expert in the technic of its use in this way report satisfactory results, it is not suited for general practice because of the grave dangers which it involves.

Attention has been called to the fact that shock may result from severe and extensive injuries to nerves during surgical operations under ether or chloroform. Cocain causes complete paralysis of the nerve-trunks if applied to them or to the nerve-endings, and thus prevents the passage of impulses through the nerves. In this way the danger of shock during operation may be lessened, even when it is necessary to combine the local anesthetic action of cocain with a general anesthetic, such as ether.

Wine of coca has been used as a general tonic, but there seems to be no indication for the use of such a preparation. Of course, any wine of coca must contain cocain, otherwise it is not wine of coca.

DOSAGE

The dose of cocain hydrochlorid for internal administration is said to be 0.03 gm. ($\frac{1}{2}$ grain). This, however, must be considered rather as a guide to the limits of safe administration than as any indication of the amount required for systemic effects, for even when taken orally for the relief of pain in gastric ulcer or to allay nausea and vomiting, it is used for its local action, and a systemic effect is undesired. On the contrary, when it is applied locally or taken internally it is desirable to delay absorption so far as possible.⁵

5. It is possible that the systemic action of cocain might be useful in enhancing the effect of epinephrin in shock, but the technic of its use for this purpose has not been developed.

It stimulates the psychic and other centers, including that of respiration, but we have safer and better drugs for those purposes.

The amount of cocain administered at any one time should be limited to 0.06 gm. (1 grain), unless its absorption can be prevented.

It is used in solution containing from 1 to 2 per cent. for the relief of pain and in 4 per cent. solution where it is necessary to induce complete anesthesia, as in cutting operations. Anesthesia of the mucous membrane and other parts of the eye which are subjected to cutting may be induced within ten minutes; this lasts about fifteen minutes and then disappears, so that the time allowed for operation is brief.

It is difficult to produce anesthesia of the nose, throat and larynx, and strong solutions are sometimes employed, but these are not devoid of danger. In laboratory experiments on dogs it was found to be impossible to produce complete anesthesia of the esophagus by applying dilute solutions, and when stronger solutions were used absorption occurred to such an extent that toxic symptoms invariably resulted. One difficulty encountered was due to the presence of an abundant secretion of mucus, which interfered with the direct application of the cocain. This difficulty may be overcome in part by the application of atropin in suitable cases.

Solutions varying from 0.5 to 4 per cent. are used for subcutaneous injection; but Schleich suggested the use of solutions of different strength (and containing morphin, without sufficient reason) for the infiltration method. This consists in injecting a relatively large amount—up to 200 c.c. (6 fluidounces)—of a solution of 1 : 10,000 in physiologic saline through a fine needle and permitting it to permeate the tissues about the region to be operated on. Relatively smaller amounts of solutions of 1 : 1,000 may be used in the same way. The pressure of the solution on the nerves assists in the anesthetic action. The solution is injected into—not beneath—the skin at first, and then into the underlying tissues successively. This method is painful when inflammation exists, and in such cases it is

preferable to inject the solution around the trunk of the nerve which supplies the region to be incised, thus blocking impulses. It would be preferable to inject the solution directly into the sheath of the nerve-trunk, but it is difficult to do this without first exposing the nerve; hence it is better to inject the solution so that it will lie around the nerve-trunk.

Solutions containing from 0.005 to 0.03 gm. (from $\frac{1}{12}$ to $\frac{1}{2}$ grain) injected into the lumbar subdural space produce loss of perception of pain in the parts supplied by the afferent nerves of that region, while the sense of touch and the capacity for voluntary movement are retained. With large doses there is a total paralysis of the regions involved soon after the pain sensation is lost.

It is essential that the solution be prevented from penetrating along the spinal canal to the medulla, for should even a small amount of cocain reach the medulla death from paralysis of the respiratory center may result.

Aside from the danger of systemic effects with this method, there is also the disadvantage that muscular relaxation does not occur.

MATERIA MEDICA

Cocaina.—Cocain, U. S. P.

An alkaloid obtained from several varieties of coca, employed in medicine usually in the form of:

Cocainae Hydrochloridum.—Cocain Hydrochlorid, U. S. P.

The neutral hydrochlorid of the alkaloid cocain occurs as colorless crystals or a white crystalline powder, permanent in air, odorless, having a slightly bitter taste, and producing on the tongue a tickling sensation followed by numbness of several minutes' duration. Cocain hydrochlorid is very soluble (1:0.4) in water and freely soluble (1:2.6) in alcohol. It is incompatible with alkalies, sodium borate and zinc sulphate. It decomposes on standing even in sterile solution.

Solutions of cocain hydrochlorid tend to decompose when boiled, the decomposition giving rise to benzoic

acid, but the loss is insignificant when boiling is not prolonged beyond a few minutes. Solutions prepared with sterile salt solution are practically sterile if care is used.

COCAIN SUBSTITUTES

The toxicity of cocain, together with minor disadvantages, such as its instability when boiled or allowed to stand, has served as a constant stimulus in the search for suitable substitutes; among the more useful of the agents which this search has brought forth are novocain, stovain, alypin, tropacocain, orthoform-new, and others which are described in New and Non-Official Remedies.

Novocain is usually said to be from one sixth to one tenth as toxic as cocain, but the toxicity of novocain depends to an extraordinary degree on the way in which it is administered.

The injection of a barely non-fatal dose into the vein of a cat causes the respiration and heart-beat to stop immediately, with gradual recovery. Such a dose may be repeated frequently at intervals of about fifteen minutes, complete recovery apparently taking place in the intervals.

Artificial respiration and the injection of epinephrin saved a certain number of animals after the injection of doses that were 25 per cent. larger than those subsequently required to cause death.

A patient is said to have died after the subcutaneous injection of a small amount of novocain, but the details of the case could not be learned.

The anesthesia which it induces is more fleeting than that of cocain; this may be overcome by the injection of epinephrin with the novocain. Novocain is not irritant and is gaining in popularity for very short operations, especially among ophthalmologists.

Stovain is about equal to cocain in anesthetic activity, but it causes dilatation of the vessels, and where a bloodless field or the astringent action of cocain is required it must be combined with epinephrin. Alypin is closely related to stovain, over which it has no obvious advantage. Solutions of these drugs and of tropacocain may be boiled without causing

decomposition, but this does not constitute any great advantage over cocain. Orthoform-new resembles cocain in its anesthetic actions, but it is insoluble; hence it is suited mainly for application to painful ulcers; in fact, it is sometimes used for diagnostic purposes in cases of suspected gastric ulcer. When relief is afforded in such cases it is taken as evidence that the pain is due to ulcer.

OTHER MEASURES FOR INDUCING LOCAL ANESTHESIA

Magnesium sulphate has been used intraspinally for the production of anesthesia, but it is not recommended.

The injection of pure water under sufficient pressure causes anesthesia of the tissues, but it is too painful for general use.

Sensory endings in the skin may become depressed as the result of overstimulation, or irritation, by drugs, such as chloroform, which are often used in the form of liniments, and diminished sensation in the region over an abscess before it bursts is probably the result of overstimulation.

Protracted immersion of a painful part in warm water lessens its sensibility to pain, and the application of heat results in vasodilatation, which is later followed by vasoconstriction when the part is exposed to cold. The cells of tissues imbibe water during immersion and this lessens the sensitiveness to pain; such protracted immersion is especially useful in allaying itching.

Anesthesia can be produced by freezing, either by immersion in a freezing mixture of salt and ice, or, more conveniently, by spraying with a volatile substance, such as ethyl chlorid or rigolene (light gasoline).

With care the freezing with ethyl chlorid spray may be accomplished with little pain, but it is suitable only for small areas and for short operations, such as opening abscesses.

Menthol is applied externally for the relief of neuralgia and certain forms of headache, the cones or

pencils affording a convenient means of application. It is sometimes inhaled for the relief of rhinitis and sore throat, or it may be dissolved in 100 parts of liquid petrolatum and applied locally. An ointment containing from 1 to 2 per cent. of menthol may be used for the relief of itching.

It is sometimes used internally for the relief of gastric pain, but it is not especially effective.

The dose is 0.06 gm. (1 grain).

Pusey of Chicago introduced solid carbon dioxid into therapeutics in 1907. When liquid carbon dioxid is allowed to escape from a cylinder into a cone it forms a snow that may be collected and formed into pencils that must be handled cautiously. When it is pressed for a few seconds against the skin the latter is frozen, and this is followed by vesication, but not by necrosis.

Pencils or crayons of carbon dioxid snow are used for the removal of capillary nevi, warts and moles, and in the treatment of rodent ulcer, lupus vulgaris and in many other conditions.

Its employment requires a special technic that does not require further discussion here.

Phenol is actively anesthetic, and the ointment of phenol is especially useful for the relief of painful ulcers. The application of an aqueous solution to parts in which the circulation is impaired is attended with serious danger of gangrene, and numerous instances of the loss of fingers and toes from this cause might be cited. The official phenol ointment does not have this disadvantage.

Eriodictyon (*yerba santa*) abolishes the sense of taste for bitter substances; hence it is used as a syrup to mask the taste of quinin and other bitter substances.

CHAPTER IV.—ANTISEPTICS AND DISINFECTANTS

Antiseptics have long been used for the preservation of the human body after death and for other purposes. Of course the nature of their action was not understood in early times. The modern use of antiseptics and disinfectants in surgery dates from their employment by Lister less than thirty-five years ago.

Lister's brilliant results aroused the hope that all pathologic micro-organisms in the human body might be killed, especially those in the blood. Though this hope has not been fulfilled it has been fostered by manufacturers of proprietary preparations, and there are few branches of the materia medica in which there have been more misunderstanding and deliberate misrepresentation.

The difficulty of destroying micro-organisms in the body tissues is shown by the results obtained by Bechhold and Ehrlich in their experiments with a large number of agents, including numerous halogen combinations with benzene derivatives. Some of these compounds were extraordinarily active against certain organisms in the test-tube, but they were uniformly ineffective in much greater concentration when used in the body. The fact cannot be reiterated too emphatically that test-tube demonstrations of disinfectants and antiseptics, however brilliant, afford no index of therapeutic value when the agents are used internally against infection in man.

The subject of antisepsis and disinfection⁶ concerns the public health and general welfare deeply; therefore the physician should understand the general prin-

6. There has been so much confusion regarding the use of the terms "antiseptic," "disinfectant" and "deodorant," that it may be permissible to define these terms briefly. A disinfectant is an agent that destroys micro-organisms. An antiseptic prevents the growth of micro-organisms so long as certain conditions are maintained. Deodorants absorb or destroy odors: they are not necessarily antiseptic or disinfectant.

ciples involved in the use of disinfectants outside of the body, and he should, of course, understand the actions of those antiseptics and disinfectants that he uses internally.

It is obvious that all disinfectants will prevent the growth of bacteria, but for some reason the fact is often overlooked that an antiseptic does not prevent the subsequent growth of the micro-organisms when the necessary conditions have changed.

The importance of this lies in the fact that antiseptics are often recommended for use where disinfectants alone are of value. It is obviously useless to employ an antiseptic in washing an infant's nursing-bottle and its fittings, because an antiseptic wash is no better than water for removing bacteria, and unless they are removed or destroyed they will multiply when the bottle is filled with milk, which is an excellent culture medium.

Anything that renders the conditions unsuitable for the growth of bacteria will act as an antiseptic, but a chemical substance, to be actively disinfectant, must penetrate the bacterial cell and act on its protoplasm. Some of the more intensely active antiseptics have been mistaken for disinfectants when tested carelessly, because enough of the antiseptics were transferred to the culture mediums with the bacteria to prevent further growth, leading to the supposition that the bacteria had been killed.

The activity of disinfectants is altered by so many different conditions that it is not sufficient to know the actual or relative degree of activity of a given agent when it is used in a test-tube experiment under the most favorable conditions; it is necessary to know also the approximate activity under the conditions in which it is to be used.

Different organisms manifest wide differences in their resistance to the action of disinfectants, and among the factors which influence the destructive activity of a disinfectant for a given organism are temperature, the presence of organic matter, and the manner of cultivation of the organism. It is obvious that we cannot accurately determine the activity of any disinfectant in a given condition, except by actu-

ally testing it under approximately similar conditions; but the standardization of a disinfectant affords an approximate indication of its value.

Of the numerous methods proposed for standardizing disinfectants, the one known as the "Hygienic Laboratory phenol coefficient"⁷ has been adopted as the basis for purchasing disinfectants by the United States government and is approved by the Council on Pharmacy and Chemistry. Stated briefly, this method consists in comparing the activity of the agent to be tested with that of phenol under conditions which seem best calculated to indicate its usefulness.

For convenience of discussion, we shall classify the antiseptics and disinfectants arbitrarily as derivatives of benzene, urinary disinfectants and antiseptics, and general disinfectants and antiseptics. The discussion cannot be either systematic or comprehensive, but it is intended to call the physician's attention to the dependable resources at his command for internal use, and for such disinfection as the general practitioner may be called on to conduct in emergencies. Many of the derivatives of benzene may be used for general disinfection, and some of those classified as general disinfectants may be used internally.

DERIVATIVES OF BENZENE

Benzene (C_6H_6) is not actively disinfectant, but phenol, which results from the substitution of an OH for an H of benzene, is sufficiently active to be used as the standard for comparison of disinfectants, though it is far from being the most active even of this group.

The toxicity of phenol (carbolic acid) lessens its field of usefulness, but the introduction of certain molecular groups into the phenol molecule lessens its toxicity without diminishing its disinfectant action. Many compounds formed in this way are now used.

Phenol combines with protein and precipitates it from solution. When applied to the skin, it forms a white eschar by precipitating albumin, with which it

7. Hygienic Laboratory Bulletin 82, April, 1912, is devoted to a discussion of this method and of the value of a large number of disinfectants which are advertised widely.

does not form a stable combination, and from which it may be removed by washing with alcohol or glycerin, in which it is very soluble.

The official phenol ointment is not actively disinfectant, because the phenol is more soluble in fat than in the bacterial cells and does not penetrate the latter. It is anesthetic, however, because the fat penetrates the skin and permits the phenol to come in contact with the sensory nerves.

The high mortality, especially from tetanus, following infected wounds, in soldiers who were not treated for some time, stimulated the search for a convenient antiseptic dressing for use in emergencies. As a result of preliminary experiments an ointment, consisting of 1 part of phenol and 4 parts of lanolin, has been recommended for the purpose.

Only those antiseptics that diffuse readily from the ointment base into the tissues should be used in this way. Experiments on animals seem to show that phenol, tricresol and thymol have the necessary diffusibility when used in 10 to 20 per cent. strength; but these have not been tested clinically, and while they may be used in emergencies, their use should not be permitted to interfere with other, and better, methods of prophylaxis and treatment.

A 25 per cent. solution of phenol in glycerin is recommended for cauterizing wounds, such as those caused by toy pistols, where there is reason to fear infection with tetanus bacillus. The wounds should be cleansed first, of course.

Liquefied phenol is sometimes used without dilution for cauterizing wounds when there is reason to fear tetanus infection. It kills the spores in a few minutes, and the pain induced is neither severe nor lasting. Phenol diluted with 20 parts of water is unfit for the purpose because it requires twelve hours or longer to kill tetanus spores.

Iodin is said to be equally effective against the tetanus spores, but it causes severe and lasting pain.

The application of pure phenol or concentrated aqueous solutions to the skin causes pain followed by anesthesia, but the use of dilute solutions is not

attended with severe pain. Oily solutions are preferable to aqueous when anesthesia is desired, but the aqueous are sometimes applied to infected superficial wounds for their antiseptic action. The water evaporates, requiring frequent renewal of the solution, and this may lead to gangrene even when dilute solutions are applied to the extremities in which the circulation is poor, as it is frequently after injuries; it is better, therefore, to add a little glycerin to the solution to retard the evaporation of the water.

Concentrated ointments and solutions of phenol should not be used, as a rule, the official 2 per cent. ointment probably being as useful for most purposes as those containing higher percentages of the anesthetic.

Fatal doses of phenol depress the central nervous system, causing profound collapse, which is usually preceded by stimulation of the cord, with increased reflexes and possibly with convulsions. Consciousness is usually retained until late in the course of poisoning, and the condition of the patient may be compared to that of one suffering from surgical shock.

Phenol is absorbed at first fairly rapidly from the alimentary tract, but after the absorption of a large, but not fatal, dose it proceeds more slowly, apparently because of interference with the circulation; hence if the stomach is washed even after severe symptoms of poisoning have developed, a part of the phenol may be removed and the patient's life be saved.

When phenol remains in the stomach bland oils are contra-indicated, because they favor its absorption, but they may be used after the stomach has been washed. White of egg should be administered immediately if it is at hand, but no time should be lost before washing out the stomach with water. Ten per cent. of alcohol may be added to the water if it does not entail loss of time, but no chemical antidote is comparable in effectiveness to the prompt washing with water in abundance. White of egg may be administered after completing the washing, as it serves the double purpose of combining with any remaining phenol and protecting the irritated mucous membrane. One should not permit any theoretical considerations

of the antidotal nature of various chemical substances to interfere with the thorough washing of the stomach with water, and when this has been accomplished (the last washing should have little or no odor of phenol), attention should be paid to methods of restoration, stimulation being required if the patient is in collapse.

Concentrated phenol causes corrosion of the esophagus and stomach if it is not removed promptly, and a bland oil, such as sweet oil, is useful to allay the pain *after* the poison has been removed.

Sodium sulphate was long supposed to be an effective antidote to phenol, with which it was said to form a sulpho-carbolate. This reaction does not occur in the body, and one should avoid being misled by this popular fallacy.

Concentrated phenol "burns" on the skin are treated by washing with alcohol or glycerin, and applying an emollient or ointment.

This peculiar white eschar or "burn" is frequently seen on the hands or about the lips of those who have taken phenol by accident or with suicidal intent, and it serves as a guide to the identification of the poison; in such case the treatment of phenol poisoning should be instituted without delay. The odor is characteristic, and it may be detected on the breath in many cases of poisoning.

SALICYLIC ACID AND SALICYLATES

Salicylic acid differs from phenol by having an H of the latter replaced by the group COOH. Benzoic acid differs from phenol by having the OH of the latter replaced by COOH. Salicylic acid is obtained from oil of sweet birch, or oil of wintergreen, both being composed mainly of methyl salicylate. It is also prepared synthetically from phenol. Benzoic acid is obtained from benzoin and prepared synthetically.

The actions of salicylic acid resemble those of phenol in a general way, but it is less depressant to the central nervous system.*

Large therapeutic doses induce symptoms resembling those caused by quinin, and with still larger doses there may be actual narcosis. The toxic symptoms include dizziness, roaring in the ears, a sense of fulness

in the head perhaps with headache, and sometimes mental dulness.

Disturbances of hearing are usually transient but sometimes lasting; they are attributable to circulatory disturbances, as are those of vision, but in the more serious cases there may be injury to the nerve cells in the ear. The respiration becomes rapid with large doses, and respiratory failure ensues in fatal cases.

Circulatory disturbances result from the action on the vasomotor centers and partly from the injury to the heart, but the toxic action on the heart is not important except with the largest doses. The vessels of the skin dilate, and sweating is often profuse, the action being similar to that seen with the other drugs of the antipyretic group. The blood pressure falls with the appearance of other symptoms of collapse, when very large doses are administered.

Salicylic acid is absorbed and circulates as a salicylate, probably as sodium salicylate, which is only feebly antiseptic, and there is much uncertainty concerning the mechanism of its action in relieving the pains of articular rheumatism. It has been suggested that salicylic acid has a specific action on the organisms which cause rheumatism, but there is no clear evidence of this. Relapses are more common in those cases in which salicylates are used than in untreated ones.

Salicylic acid and sodium salicylate are irritant to the stomach, and it is customary to administer an excess of alkali with it, preferably sodium bicarbonate, to prevent liberation of the acid by the gastric juice.

Many efforts have been made to prepare substitutes for salicylic acid which would be devoid of the action of the latter on the stomach and central nervous system, while retaining its therapeutic actions. These efforts have been somewhat more successful with regard to obviating the local irritant action on the stomach than with reference to the systemic effects. Several of these substitutes will be discussed later.

The relative value of salicylic acid and the synthetic substitutes for it constitutes a question apart from that of the relative toxicity of salicylic acid itself prepared synthetically and that obtained from oil of

wintergreen or oil of sweet birch. There has long been current a mistaken belief that the natural salicylic acid is less toxic than the synthetic product. This belief arose from the fact that early reports were to the effect that the synthetic product contained very poisonous impurities; but recently an extended investigation of the subject was undertaken by the Council on Pharmacy and Chemistry, and comparative results obtained with the natural and synthetic products were reported; these reports were reviewed by W. A. Hewlett, who summarized the results obtained by fifteen clinicians in the treatment of 139 patients. Hewlett reports that there is no difference between the natural and the synthetic salicylic acid so far as observable results are concerned.⁸ The natural salicylic acid is many times as expensive as the synthetic.

It is commonly stated that salicylates increase the elimination of bile, but this action is probably unimportant therapeutically.

SALOL

Among the various compounds which have been introduced with a view to lessening the toxicity of salicylic acid is phenyl salicylate, or salol, as it is commonly called, consisting of one molecule of salicylic acid united to one of phenol. This is almost insoluble in the gastric juice; hence it does not irritate the stomach; but passing into the intestine, it is decomposed with the liberation of its component parts, the salicylic acid combining with sodium salts to form sodium salicylate, this and the phenol being absorbed.

Salol lacks the disagreeable taste of sodium salicylate, and it does not irritate the stomach; but its actions are obviously those of phenol and sodium salicylate, though these actions are slowly developed.

Human milk is said to contain a ferment capable of splitting salol, and gastric irritation is reported to have occurred in some cases when salol was administered to breast-fed infants.

⁸ Hewlett, A. W.: Clinical Effects of "Natural" and "Synthetic" Sodium Salicylate, *Jour. Am. Med. Assn.*, Aug. 2, 1913, p. 319.

ACETYL-SALICYLIC ACID

Acetyl-salicylic acid (aspirin) is formed by the introduction of the acetyl group into salicylic acid. It is less irritant to the stomach than salicylic acid. It is decomposed in the intestine with the formation of acetates and salicylates; hence its systemic actions are those of salicylic acid.

ATOPHAN

Atophan acts on the kidney, causing some increased secretion of urine but a relatively greater increase in the elimination of uric acid, and some increase in the total nitrogen and ammonia. There is no evidence that it has any influence on the urates deposited in the body or that it increases the formation of uric acid.

Through its action, the uric acid of the blood may be diminished one half on a purin-free diet, and when the diet contains purins, the amount of uric acid in the blood may be maintained at a normal level.

It is said that uric acid is eliminated so rapidly that it may form deposits in the urinary tubules unless an abundant diuresis is maintained; hence the patient is advised to drink an abundance of water during the time that the atophan continues to act.

The action begins promptly, reaches its maximum within about three hours, and usually is nearly over in nine hours.

Atophan relieves the pain of acute gout, and is said to be devoid of disagreeable side actions.

It has a slightly bitter taste. Atophan and several closely related compounds are described in New and Nonofficial Remedies.

BENZOIC ACID AND BENZOATES

Benzoic acid differs from salicylic acid in having no phenolic OH group. It is obtained from benzoin and prepared synthetically. Benzoic acid and the benzoates are almost devoid of toxicity for the central nervous system, but they are also much less actively antiseptic and only feebly disinfectant.

The wide-spread use of the benzoates as food preservatives has led to discussions which at times have

been more acrid than scientific. We do not know that benzoates are distinctly harmful to healthy adults when taken in moderate amounts even for prolonged periods, but we have no knowledge of their effects on those who are not in good health. Hence it is preferable to avoid the constant use of benzoates in foods.

If one cannot speak in unqualified condemnation of the use of food preservatives at all times, there can be no question of the undesirability of using them to cover up and hide the renovation of partially decomposed foods.

Food preservatives are sometimes used fraudulently, and for such abuses there can be no extenuation; but Long has recently directed attention to the prejudice existing against the use of "chemicals" as food preservatives, despite the fact that smoked meats are preserved by very active chemicals, and that potassium nitrate has long been used as a preservative without a hint of its being injurious.

He believes that unreasoning prejudice prevents our forming a just estimate of the value of many food preservatives and the benefits that are to be derived from their proper use.

Benzoic acid has no important therapeutic uses, so far as its internal administration is concerned. It may be used as a mild antiseptic.

CRESOLS

The cresols differ from phenol by having a methyl group— CH_3 —replacing an H of phenol. The official cresol consists of a mixture of three isomeric cresols. Only one of these is desired for its antiseptic action, but it is expensive to separate them; hence the mixture is used where a cheap but efficient disinfectant is desired.

Its action resembles that of phenol, but it is less poisonous and about four times as actively germicidal. It has the disadvantage of not mixing readily with water; hence it is commonly employed in a mixture with an equal amount of potassium soap, known as compound solution of cresol. This is useful for dis-

infecting the skin, for lubricating the hands and as a vaginal douche. It is inexpensive and may be used for disinfecting rough furniture and rooms which are not injured by washing with soap and water.

Cresol is used as a disinfectant in solutions of 0.25 to 1 per cent. The compound solution is used in 1 to 5 per cent. solutions for washing wounds and as a douche.

CREOSOTE

Creosote is a mixture of phenols and phenol derivatives, including guaiacol and creosol, obtained from beechwood tar.

The systemic actions of creosote resemble those of phenol, but it is credited with being useful as an intestinal antiseptic, and its beneficial effect in the treatment of tuberculosis has been explained as due to this intestinal antiseptis. The odor of creosote in the breath after it had been taken gave rise to the belief that it acts as an antiseptic in the lungs, but it has no destructive action on the tubercle bacilli in the lungs, because they are embedded in the tissues and are therefore inaccessible to the creosote.

GUAIACOL

Guaiacol is one of the chief constituents of beechwood creosote, which it resembles closely in its actions. It is somewhat less actively antiseptic and germicidal.

It is absorbed from the unbroken skin, and is then capable of reducing the body temperature, but it is prone to cause collapse.

It is used much like creosote, over which it has no decided advantages.

The carbonate of guaiacol is a crystalline powder, which is inactive until it is decomposed with the liberation of guaiacol. It is said that this decomposition takes place only in the presence of putrefactive organisms, and that its antiseptic action is developed only where it is needed.

Its tastelessness and the decomposition in the presence of putrefactive organisms would seem to give it a decided field of usefulness.

THYMOL

Thymol is a phenol obtained commercially from oil of ajowan and occurring in oil of horsemint, oil of thyme and other volatile oils. It is frequently used as a urinary antiseptic and of late it has come into considerable prominence as a remedy in hookworm disease.

Thymol iodid, formerly known as aristol, is an antiseptic powder which was supposed to represent the activities of thymol and of iodine, but it is so stable that it has little of the actions of either. There seems to be no sufficient reason for its continued use as a substitute for iodoform, to which it is inferior in antiseptic action. It is nearly odorless; at least, the odor is not nearly so penetrating as is that of iodoform.

It is used as a dusting-powder.

This may be taken as representing the type of preparations which have been introduced as substitutes for iodoform, in which it is sought to secure the antiseptic action of the latter without its disagreeable odor. Many of these preparations have been introduced, but they are not antiseptic unless they are decomposable with the liberation of iodine. Most of them have fallen into disuse, or are employed as dusting-powders, for which purpose they have no advantage over much less expensive ones.

Betanaphthol, also known as naphthol, is a phenol found in coal-tar, but usually manufactured from naphthalene. It is only sparingly soluble in water (1:950) and is absorbed rather slowly from the alimentary tract. When absorbed in sufficient amounts it is capable of inducing toxic effects, including nephritis and destruction of the red blood corpuscles.

It is more actively antiseptic than phenol, and has been used as an intestinal antiseptic; for this purpose its slight solubility and absorbability are advantages.

H. C. Wood, among others, has called attention to the large volume of fluid which the intestines contain—variously estimated at from 4 to 6 liters—and the large amount of antiseptics which would be required to be effective. While the intestinal antiseptics in common use may exert their action in the small intes-

tine, it seems extremely doubtful whether any of those discussed so far can be administered in sufficient amount to influence the contents of the large intestine to a marked degree.

The subject of intestinal antiseptics by means of drugs intended to inhibit the growth of bacteria has received a great deal of attention, but the results hitherto reported are contradictory and difficult to explain.

There can be no doubt that the nature and character of the infection, its location in the intestinal tract, and the condition of the intestinal mucous membrane and its secretions, as well as the food residues in the bowel, must all influence the results of any efforts at intestinal antiseptics.

It is not certain that absolute asepsis of the intestine is desirable, though it is unquestionably desirable to restrain the growth of putrefactive and other pathologic organisms.

The administration of a brisk cathartic at a time when the body has not suffered serious injury from the toxins of the organisms serves to sweep out enormous numbers of bacteria mechanically, but unfortunately many remain, and if conditions favor their development there will soon be as many as before, for the number which results in one day from the unrestrained development from a single bacterium is inconceivably great.

It is a matter of common experience that calomel affords greater relief in the condition commonly called "biliousness," than do other drugs of equal purgative activity. This can be understood readily when one remembers the various ways just mentioned in which the development of bacteria may be influenced.⁹ Others find a brisk saline cathartic more satisfactory in relieving the headaches and depression which are commonly associated with some form of bacterial activity in the intestine.

Attempts to modify the bacterial flora have been made by introducing cultures of lactic acid bacilli, the idea being that they will multiply and, splitting sugar,

9. Intestinal Antiseptics is discussed by Norman M. Harris in Jour. Am. Med. Assn., Oct. 12, 1912, p. 1344.

form lactic acid, which is inimical to putrefactive organisms. This method appears to be attended with some success at times, but the lactic acid bacilli die off rapidly and must be taken constantly for prolonged periods to be of any service.

Numerous forms of this culture are described in New and Nonofficial Remedies.

THERAPEUTIC USES

One part of phenol in five hundred or a thousand parts of water is actively antiseptic for most of the common pathogenic bacteria, and a 1 per cent. solution is actively germicidal for nearly all of the nonsporulating forms, destroying them in a few minutes at ordinary temperatures. Anthrax spores, however, are not destroyed by a 5 per cent. solution in twenty-four hours, and tetanus spores are almost as resistant.

Phenol is applied to the skin in dilute solution or preferably as an ointment to relieve itching as in piles. It is also useful as an application to small painful ulcers. The statement is often made that the pain of burns is increased by phenol ointment, but such increase of pain is transient and an anesthetic action is then obtained. Phenol cannot be applied to large surfaces because of the danger of absorption.

It is often used as an antiseptic in the form of gargles, and mouth-washes, but in such cases it can have little value as an antiseptic. Any benefit derived must be due to the allaying of irritation and the cleansing of surfaces, for phenol cannot be kept in contact with the bacteria long enough to have any important influence on their multiplication.

It is said to be of some value in vomiting. This is probably explained by its capacity for lessening the irritability of the gastric mucous membrane, by its anesthetic action. In that case it can have little more than momentary value. It has been used to relieve gastric fermentation, but it is not recommended for this purpose.

The antiseptic and disinfectant uses of many of the agents which have been discussed require no further consideration. Salicylic acid, the salicylates, including

salol and aspirin, and the other derivatives of salicylic acid, are used widely for the relief of joint symptoms in articular rheumatism, and for the reduction of fever which attends that condition. Salicylic acid has no influence on the endocarditis that accompanies rheumatism so frequently, however, and, as previously stated, it does not prevent the recurrence of the rheumatic attacks.

The salicylates afford relief in rheumatism only while medication is continued. They are used for the relief of headache and other neuralgic affections, in chorea, in tonsillitis and in various catarrhal inflammations.

The salicylates cause some increase in the excretion of uric acid. For this reason, perhaps, they have been used in gout, but they are of little value in that condition. There is no evidence that any slight influence which they may have on the secretion of bile is of value in the treatment of constipation. Sodium salicylate is said to be useful in certain conditions of the eye, including iritis, keratitis and glaucoma.

The caustic action of salicylic acid is utilized for the removal of corns and calluses.

Large doses of the salicylates are contra-indicated late in the course of pregnancy because of their tendency to produce abortion.

Phenyl salicylate, or salol, is said to have an especial field of usefulness as an antiseptic in diarrhea and enteritis.

Its comparative insolubility in the gastric contents has led to its employment for coating pills intended to pass through the stomach and dissolve in the intestine, but the amount required to coat one or two large pills constitutes very nearly a full therapeutic dose.

DOSAGE

Phenol is crystalline at room temperature, and owing to the inconvenience of handling it, the liquefied phenol is usually employed. The dose of the liquefied phenol is 0.05 c.c. (1 minim), corresponding to about 0.04 gm. ($\frac{1}{5}$ grain) of the crystalline.

Salicylic acid is seldom administered as such internally, sodium salicylate being commonly employed, or

methyl salicylate (oil of sweet birch or oil of winter-green) or aspirin may be used.

Methyl salicylate and sodium salicylate are usually given in doses of 1 gm. (15 grains), which may be repeated every hour or every two hours until the maximum permissible amount is given. This is indicated by ringing in the ears, perhaps some dizziness, and occasionally some slight mental disturbance such as confusion.

About 6 to 8 gm. (90 to 120 grains) are usually required to induce the symptoms indicative of the limits of tolerance, but if the larger amount fails to induce the usual symptoms, the dose may be given less frequently, or a smaller dose every two hours. After the symptoms appear the administration is usually limited to about three doses per day.

For headache and neuralgia much smaller amounts are employed, 1 gm. (15 grains) being usually sufficient.

Phenyl salicylate, or salol, is given in smaller amounts than is sodium salicylate because of the danger of phenol poisoning from such large doses. For whatever purpose salol is used, the dose should not usually exceed 0.5 gm. (8 grains).

Aspirin, or acetylsalicylic acid, is given in somewhat smaller doses than is sodium salicylate in the treatment of rheumatism, the symptoms which indicate the limits of dosage being the same as with sodium salicylate.

It is given in doses of 0.3 gm. (5 grains) for the relief of headache.

The dose of atophan is 0.5 gm. ($7\frac{1}{2}$ grains).

Benzoates might be given in larger doses than the salicylates were there any occasion to administer them internally.

Cresol is not often used internally, but the dose is said to be 0.05 c.c. (1 minim).

Creosote is given in doses of 0.2 c.c. (3 minims) three times daily, but it should be discontinued when it disturbs the appetite and digestion.

Guaiacol is given in doses of 0.1 c.c. ($1\frac{1}{2}$ minims) in an emulsion or dissolved in a bland oil contained in capsules, and if this dose is borne without disturbance

it may be increased cautiously to 0.6 c.c. (10 minims). The carbonate of guaiacol may be given more boldly, since it is inactive until it is decomposed, the dose being 1 gm. (15 grains). It is incompatible with alkaline hydroxid.

The dose of thymol for ordinary purposes is said to be 0.1 gm. ($1\frac{1}{2}$ grains), but in the treatment of hookworm disease, it must be used more boldly.

It is especially necessary to prevent its absorption when large doses are used; hence oils and fats should be avoided in the diet.

Betanaphthol is used in doses of 0.1 to 0.3 gm. ($1\frac{1}{2}$ to 5 grains).

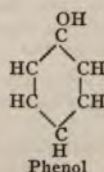
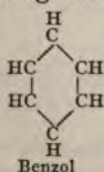
If the intestinal contents measure as much as 4 liters, the larger dose mentioned above would constitute a dilution of one part of betanaphthol in about thirteen thousand parts of the contents—a dilution in which its antiseptic action is extremely feeble at best. Such a dose probably has little antiseptic action beyond the small intestine.

Betanaphthol is sometimes used externally in the form of an ointment.

MATERIA MEDICA

Phenol.—Phenol, U. S. P.

Phenol, or, as it is more popularly known, carbolic acid, is hydroxy-benzene and may be obtained either from coal-tar by fractional distillation and subsequent purification or made synthetically by replacing one hydrogen of benzol by a hydroxyl group as shown in the following formula:



The official article is required to contain not less than 98 per cent. of phenol ($\text{C}_6\text{H}_5\text{OH}$). It occurs as small colorless deliquescent crystals which are liquefied by the addition of about 8 per cent. of water. The official preparation:

Phenol Liquefactum.—Liquefied Phenol, U. S. P., contains about 86.4 per cent. of phenol and about 13.6 per cent. by weight of water and remains liquid at ordinary room temperatures. Phenol is soluble (1:20) in water and miscible in all proportions with alcohol or glycerin.

Acidum Salicylicum.—Salicylic Acid, U. S. P.

Salicylic acid ($\text{HC}_7\text{H}_5\text{O}_2$) exists, in combination, in various plants but is generally prepared synthetically from phenol. It occurs as white needle-shaped crystals or as a crystalline, odorless powder possessing a sweetish, subsequently acrid, taste. Salicylic acid is only slightly soluble (1:308) in water, but freely soluble (1:2) in alcohol or ether.

Sodii Salicylas.—Sodium Salicylate, U. S. P.

Sodium salicylate occurs as white pearly scales or as an amorphous powder; the commercial product usually has a slight buff or pink tint. It is odorless and has a sweetish taste. It is very soluble (1:0.8) in water and freely soluble (1:5.5) in alcohol. Sodium salicylate is preferably administered in solution or in gelatin capsules. The widely used compressed tablet may act as an irritant, if given on an empty stomach, producing nausea, and occasionally, vomiting. A mixture of sodium salicylate with sodium bicarbonate in the form of an effervescent draught is an acceptable method of administering the salt. The following prescription may be used for a mixture of this kind:

	gm.	
R Acidi salicylici.....	10	3 iiss
Sodii bicarbonatis.....	20	3 v
Misce et fac chartulas xx.		

Sig.: Dissolve the contents of one paper in half a glass of water and drink as effervescence is about completed.

If an effervescent mixture is not desired, equal parts of sodium salicylate and sodium bicarbonate may be directed to be dispensed in the form of a "shake" mixture with water; care should be taken to have it recently prepared, as the alkali tends to decompose the sodium salicylate on standing.

Methylis Salicylas.—Methyl Salicylate, U. S. P.

An ester of salicylic acid ($\text{CH}_3\text{C}_7\text{H}_5\text{O}_3$) which occurs in oil of sweet birch and oil of wintergreen, or which may be produced synthetically, the products from the three sources being identical, and there is no reliable method of differentiating between them.

Pure methyl salicylate is a colorless liquid having a characteristic strongly aromatic wintergreen odor and a sweetish, warm, aromatic taste. It is nearly insoluble in water but is miscible in all proportions with alcohol and the fatty oils.

For internal use methyl salicylate or either of the natural oils is best directed to be dispensed in capsules. It is also readily absorbed from the skin and is frequently applied in the form of a liniment. A type prescription for this kind of application is the following:

	c.c.	
R Methylis salicylatis		
Linimenti saponis.....āā	50	℞ xii
M. Sig.: Use as a liniment.		

The soap liniment in the foregoing formula may be replaced by one of the fatty oils like olive oil, or, if an additional counter-irritant is desired, by chloroform liniment.

Phenylis Salicylas.—Phenyl Salicylate, U. S. P.—Salol.

The salicylic ester of phenyl ($\text{C}_{13}\text{H}_{10}\text{O}_3$) occurs as a white crystalline powder having a faint aromatic odor and a slight but characteristic taste. It is very slightly soluble (1:2,333) in water but freely soluble (1:5) in alcohol. Phenyl salicylate or salol is best administered in the form of powder or recently prepared capsules.

Salol has such a low melting point that a pill or tablet made of it may fuse into a solid mass without material change in its appearance, but it then dissolves very slowly in the intestinal tract and may traverse it and be voided in the stool.

Acetyl-Salicylic Acid.—Aspirin, N. N. R.—Acetyl-salicylic Acid.

The acetyl derivative of salicylic acid, aspirin, occurs as a crystalline odorless powder having a faint acidulous taste. It is slightly soluble (1:300) in water

and freely soluble (1:5) in alcohol, ether or chloroform. Because of its slight solubility aspirin is best prescribed in the form of capsules or catchets.

Atophan.—Atophan, N. N. R., phenyl-quinolin-carboxylic acid, $C_9H_5N.C_6H_5COOH$, was first described by Doebner and Giesecke in 1887, but has been introduced into therapeutics only recently. It occurs as colorless needle-shaped crystals; it is practically insoluble in water, but readily soluble in solutions of alkalis and in hot alcohol.

Acidum Benzoicum.—Benzoic acid, U. S. P.

An organic acid obtained from benzoin by sublimation or prepared synthetically, preferably from toluol. It occurs as colorless or almost colorless scales or needles having an agreeable characteristic odor and a pungent acid taste. It is only slightly soluble (1:400) in water but is freely soluble (1:2) in alcohol. It reacts with alkali hydroxids and carbonates to form water-soluble benzoates, the best known of which is:

Sodii Benzoas.—Sodium Benzoate, U. S. P.

Sodium benzoate occurs as a white, amorphous, odorless powder having a sweetish, astringent taste. It is freely soluble (1:2) in water and soluble (1:43) in alcohol.

Cresol.—Cresol, U. S. P.

A mixture of the three isomeric cresols obtained from coal-tar. Cresol occurs as a straw-colored, refractive liquid, having a phenol-like odor and turning yellowish-brown on exposure to the air. It is soluble (1:60) in water and miscible in all proportions with alcohol, petroleum benzin, ether or glycerin. It is also miscible with soap solutions and with solutions of alkali hydroxids, and in this combination represents an economic type of disinfectant. It is at the present time widely employed in the form of:

Liquor Cresolis Compositus.—Compound Solution of Cresol, U. S. P.

This is a combination of equal parts of cresol and a solution of potassium soap which is miscible in all proportions with distilled, or ordinary soft, water. This compound solution of cresol has about twice the

germicidal power of pure cresol, and on account of its saponaceous character may be used for washing walls, floors, and other articles not injured by ordinary soap and water.

Creosotum.—Creosote, U. S. P.

A mixture of phenols and phenol derivatives, chiefly guaiacol and creosol, obtained during the distillation of wood-tar. Creosote occurs as a colorless or slightly yellowish oily liquid having a penetrating smoky odor and a burning, caustic taste. It is slightly soluble (1:400) in water and miscible in all proportions with absolute alcohol and the fixed and volatile oils. It is difficult to administer creosote in any form not objected to by the patient, because of its rather disagreeable odor and taste. A mixture of creosote and a fixed oil like olive oil dispensed in the form of an emulsion or in capsules is perhaps the most acceptable method of administration. Smaller quantities of creosote can also be administered in the form of pills, or capsules, by absorbing the creosote in powdered glycyrrhiza.

Guaiacol.—Guaiacol, U. S. P.

One of the chief constituents of creosote obtained by collecting and purifying the fraction boiling between 200 and 205 C. (392 and 401 F.); also prepared synthetically. Pure guaiacol at low temperatures occurs as a colorless or nearly colorless crystalline solid which melts at 28.5 C. (83.3 F.). It has an agreeable aromatic odor and a burning, caustic taste. It is soluble (1:53) in water and miscible in all proportions with alcohol and the fixed and volatile oils. Guaiacol shares with creosote the difficulty of internal administration, and like that preparation is best directed to be mixed with a bland fixed oil or an absorbent powder and dispensed in the form of capsules.

Guaiacolis Carbonas.—Guaiacol Carbonate, U. S. P.

The carbonic ester of guaiacol ($C_{15}H_{14}O_5$) occurs as a white crystalline powder of neutral reaction, almost odorless and tasteless. It is practically insoluble in water, but is soluble (1:48) in alcohol. It is readily decomposed in the presence of alkalis into

guaiacol, and is best directed to be administered alone in the form of capsules, cachets or loose powder.

Thymol.—Thymol, U. S. P.

Thyme camphor, or isopropyl-metacresol, is a crystalline phenol, obtained commercially from oil of ajowan (produced from an umbelliferous seed grown in India), and found in a number of other volatile oils. Thymol occurs as large colorless crystals having an aromatic thyme-like odor and a pungent, somewhat caustic taste. It is only slightly soluble (1:1,000) in water but very soluble (1:0.9) in alcohol and readily miscible with fixed and volatile oils. For internal use it is usually directed to be administered in the form of capsules.

Thymolis Iodidum—Thymol Iodid, U. S. P.—Aristol.

Dithymol-diiodid ($C_{20}H_{24}O_2I_2$) should contain approximately 45 per cent. of iodine. It occurs as a bright chocolate-colored or reddish-yellow bulky powder having a slightly aromatic taste. It is practically insoluble in water and nearly insoluble in alcohol.

Betanaphthol.—Betanaphthol, U. S. P.—Naphthol.

Beta-hydroxy-naphthalene ($C_{10}H_7OH$) is a monatomic phenol occurring in coal-tar, but usually prepared by treating naphthalene with sulphuric acid and subsequently decomposing the naphthalene sulphonic acid thus formed.

Betanaphthol occurs as colorless or pale buff-colored crystalline scales or a crystalline powder having a faint phenol-like odor and a sharp pungent but not persistent taste. It is only slightly soluble (1:950) in water but very soluble (1:06) in alcohol. For internal administration it is usually directed to be dispensed in the form of powder or capsules, preferably in combination with bismuth subnitrate or bismuth subcarbonate.

	gm.	
℞ Betanaphtholis	1	gr. xv
Bismuth subnitratis.....	10	3 iiss
Misce et fac chartulas xx		

Sig.: One powder before meals.

For use as an antiseptic, protective ointment it may be prescribed as follows:

R	Betanaphtholis	2	gm.	
	Petrolati	30		gr. xxx
				3 i
M.	Sig.: Use externally.			

URINARY ANTISEPTICS AND DISINFECTANTS

HEXAMETHYLENAMIN

Numerous balsams, oleoresins and volatile oils were used formerly as antiseptics for the urinary tract, but these have been almost entirely superseded of late by hexamethylene-tetramin, or, as it is officially known, hexamethylenamin, which is sold under a great many different trade names, including urotropin, formin, aminoform, formamin, cystogen and many others.

Hexamethylenamin is not actively antiseptic, but it is decomposed in acid urine with the liberation of formaldehyd, which is the active agent. Hexamethylenamin has no antiseptic action in the tissue fluids or in neutral or alkaline urine. Strongly acid urine liberates the formaldehyd much more effectively than does feebly acid urine; hence it is better to use even small doses of hexamethylenamin while adopting measures to insure marked acidity of the urine than to use large doses of the drug while the urine is alkaline or only feebly acid. The acidity of the urine can be increased by the use of acid sodium phosphate¹⁰ (NaH_2PO_4). Note that this is not the official sodium phosphate U. S. P. VIII, which is disodium phosphate (Na_2HPO_4).

Since the disinfectant and antiseptic activity of hexamethylenamin depend on the liberation of formaldehyd by an acid medium, it is obvious that it can have no material antiseptic value in the spinal fluid during spinal meningitis. Large doses were used for this purpose after it had been observed that hexamethylenamin is secreted into the spinal fluid.

10. Jordan, Anson: Urinary Antiseptics, Brit. Med. Jour., Sept. 13, 1913, p. 648.

It is obvious that the hexamethylenamin should not be decomposed before it reaches the urine; hence acids and acid salts, including monosodium phosphate, and acetylsalicylic acid, should not be dispensed in mixtures with it, even though they are used simultaneously.

Hexamethylenamin is used to prevent the growth of micro-organisms in the urinary tract, and to destroy them when they are present in the urine during infectious diseases such as typhoid fever.

It is used as an antiseptic in cystitis and as a prophylactic in operations on the urinary tract. It is sometimes used to prevent nephritis in scarlet fever, but very large doses cause albuminuria.

A solution of formaldehyd is a solvent for uric acid, and on this basis hexamethylenamin has been used to dissolve calculi; but it is wholly useless for that purpose.

It is one thing to hold a substance in solution or prevent its precipitation when one uses a concentrated solution of formaldehyd, and quite another matter to dissolve calculi in weak solutions such as one may secure in the urine.

Hexamethylenamin is sometimes used in infections of the respiratory tract, but formaldehyd can be applied directly in such cases and there is no evidence that hexamethylenamin has any value in such conditions.

SILVER NITRATE

Silver nitrate is a germicide of extraordinary activity against the gonococcus. Solutions of from 1:10,000 to 1:2,000 have been used for injection into the urethra, and solutions of 1:5,000 into the bladder, but even dilute solutions are irritant to the urethra, and silver nitrate has been largely replaced in recent years by the less irritant organic silver compounds.

Surfaces should be cleansed before applying the solution, the action of which may be stopped at once by applying a solution of sodium chlorid which precipitates the insoluble silver chlorid. This should be borne in mind when solutions are prepared, and only distilled water should be used for the purpose.

Silver nitrate has come into wide-spread use for treating the eyes of the new-born to prevent infection, especially where there is reason to fear gonorrheal conjunctivitis. Immediately after the head appears on the perineum the face is wiped clean and a drop of 2 per cent. solution of silver nitrate is dropped into each eye.

It is used in various forms of conjunctivitis but it should not be used indiscriminately, as it is capable of doing much harm when used in unsuitable conditions.

Protargol, or silver proteinate, contains 8.3 per cent. of silver combined with albumin. It is used as a non-irritant substitute for silver nitrate in gonorrhea and in diseases of the eye, nose and throat.

DOSAGE

Hexamethylenamin is frequently administered in doses of 0.3 gm. (5 grains), though many practitioners prefer much larger doses, from 1 to 2 gm. (15 to 30 grains) being administered three or four times a day to patients who do not manifest the unpleasant secondary symptoms that are sometimes caused by it.

Silver nitrate is used in solutions varying from 1:50 to 1:10,000. Protargol is used in solutions up to 20 per cent. The solutions of the latter are best prepared by sprinkling the protargol on the surface of the required amount of water and allowing it to dissolve spontaneously.

Copaiba is preferably administered in the form of emulsion or capsules in doses of 1 c.c. (15 minims).

Oil of santal is usually given in doses of 0.5 c.c. (8 minims).

MATERIA MEDICA

Hexamethylenamina.—Hexamethylenamin, U. S. P.

This preparation is known and used under a variety of trade names, and in European pharmacopeias is generally recognized by its chemical title, hexamethylenetetramin ($(CH_2)_6N_4$), a product formed by the condensation of ammonia and formaldehyd with the elimination of water.

Hexamethylenamin occurs as colorless, lustrous, odorless crystals having, when in aqueous solution, an

alkaline reaction on red litmus paper. It is freely soluble (1:1.5) in water, and soluble (1:10) in alcohol. Hexamethylenamin is incompatible with acids, acid salts and combination acids like aspirin, which react with it and liberate formaldehyd. It is also incompatible with salts of ammonia, from which it separates ammonia. To avoid possible decomposition it is best administered by itself either in simple solution or in the form of powders, capsules or cachets.

Argenti Nitras.—Silver Nitrate, U. S. P.

Colorless transparent crystals, becoming gray or grayish-black on exposure to light in the presence of organic matter; odorless, but having a bitter, caustic and strongly metallic taste.

Silver nitrate is very soluble (1:0.54) in water, and soluble (1:24) in alcohol.

Copaiba.—Copaiba, U. S. P.—Balsam of Copaiba.

An oleoresin derived from one or more South American species of *Copaiba*. It is practically insoluble in water and only partially soluble in alcohol.

Oleum Santali.—Oil of Santal, U. S. P.—Oil of Sandalwood.

A volatile oil distilled from the wood of *Santalum album*. Oil of santal is frequently administered in combination with copaiba and, like that product, is best exhibited in the form of an emulsion or in capsules.

GENERAL DISINFECTANTS

Every one knows that sunlight and heat destroy all bacteria, but the limitations of these agents are not always appreciated. Direct bright sunlight shining immediately on bacteria destroys them rapidly, but when these are protected by even minute masses of dried organic matter, they may escape destruction; therefore care should be exercised when sunlight is employed as a disinfectant to see that no small masses are present with bacteria in them.

Flat surfaces of wood and cloth may be disinfected readily by exposure to direct sunlight.

Heat of sufficient intensity destroys all organisms, but small masses of organic matter may protect bac-

teria to such an extent that even boiling for a short time will fail to destroy the organisms thus protected. Tetanus spores are not destroyed immediately in boiling water, even when they are not protected.

Few organisms, even spores, resist steam under pressure for more than a few minutes. Boiling water destroys nearly all organisms within half an hour. Even moderately hot water injures the bacillus of typhoid fever, and it is destroyed almost instantly in boiling water, provided that it is not protected at such times by masses of feces or other matter. Care should be exercised to see that such masses have been dissolved or disintegrated completely before the disinfection is begun, or, at any rate, before it is completed.

HALOGENS AND THEIR COMBINATIONS

All of the halogens are actively disinfectant, but fluorin and bromin are too corrosive for general use. Chlorin is commonly used in the form of hypochlorites which yield chlorin. Iodin is used in the form of a solution or tincture, or in combination with an organic substance. Tincture of iodine is irritant, but is often applied locally for the disinfection of the skin. It is said that the skin should be thoroughly dried before the iodine is applied. Iodin is very commonly used to paint the skin at the site of a hypodermic injection, or small incision.

While there is no question of the disinfectant action of iodine *in vitro*, there is a good deal of uncertainty concerning the degree of its disinfectant activity after it comes in contact with the tissues with which it combines, for it then attacks bacteria less energetically.

Iodin is also destructive to larger parasites which infest the skin.

Among the combinations of iodine with organic substances are iodoform, iodothymol, or thymol iodide, which has been mentioned.

Iodoform is not actively disinfectant, but when applied to moist wounds, it decomposes slowly with the liberation of active iodine, partly free, and partly in unknown combinations. It is sometimes absorbed from open wounds, probably in the form of one of

these unknown compounds, and gives rise to characteristic symptoms of poisoning. The first symptoms consist in disturbances of the central nervous system; these are followed only after several days by excitement, restlessness, anesthesia and sometimes by unconsciousness. Stimulation may alternate with depression, or there may be pure narcosis.

These symptoms do not occur unless iodoform is used over large surfaces or for a considerable period of time. It is not necessary to discuss the actions of iodoform after internal administration, because there is no occasion to administer it internally.

Iodoform is applied in the form of an emulsion or as a dusting powder, especially in the surgical treatment of tuberculosis. It may be used as a suppository for the relief of painful hemorrhoids.

Chlorid of lime, so-called, which is a mixture containing hypochlorites mainly, which readily yield free chlorin, is one of the most commonly used of household disinfectants and bleaching agents. It is corrosive, attacking metals and destroying fabrics.

Chlorin is available in the form of other hypochlorites, which may be decomposed to yield free chlorin.

FORMALDEHYD

Formic aldehyd, or formaldehyd, is a very active antiseptic, but its germicidal powers vary widely with the organism and the conditions under which it is employed. It has been found that tubercle bacilli require forty-five minutes for their destruction in a 5 per cent. solution; with a higher temperature the solution is more active. The gaseous formaldehyd is not to be depended on as a germicide when the temperature is lower than 16 C. (60.8 F.).

Tightly closed rooms may be disinfected by wetting sheets with 150 c.c. (5 fluidounces) of the official formaldehyd solution for each thousand cubic feet of space, and allowing this to evaporate. The room is kept closed for twenty-four hours. The formaldehyd may be sprayed through a keyhole into the closed room, but this is inconvenient. Candles are now sold for fumigating rooms with formaldehyd, this being

the most convenient method available. Rooms may be fumigated in the way indicated, but clothing and other fabrics must be hung up so that the gas will come in contact with every portion. The room should be heated if the fumigation is carried out in winter, and the atmosphere should be kept moist by the evaporation of water. The gas does not injure fabrics.

Formaldehyd has a wide field of usefulness as a disinfectant, and the solution may be used for fabrics which may be wetted by it without injury. The irritant vapor of formaldehyd persists in the atmosphere of a room for some time after the doors and windows are opened; this disadvantage may be overcome in part by spraying a little ammonia into the atmosphere, or more conveniently, by exposing it freely on plates.

MISCELLANEOUS DISINFECTANTS

Among the cheaper disinfectants used in cesspools, drains and other large spaces are copperas, or ferrous sulphate, sulphur as brimstone or roll sulphur, which is burned in an iron pot, or other suitable container; and lime, which is used either as milk of lime to dissolve organic matter and destroy the bacteria, or as a whitewash for application to flat surfaces.

Copperas is an excellent deodorant for urinals, a handful of the crystals being thrown into the urinal and allowed to dissolve slowly.

Halsey states that sulphurous acid affords the only practical means of destroying the mosquito that carries the infection of yellow fever, and that it is commonly used in living-rooms. Burning sulphur is converted into the dioxid, and this into sulphurous acid when it comes in contact with moisture.

The fumes of burning sulphur are extremely irritating and poisonous, and they corrode metals and fabrics; hence disinfection by this means is limited to large rooms and spaces where the corrosive action will not cause damage.

Polished metal fixtures and many other articles and substances may be protected against sulphurous acid and other corrosive fumes by coating them with paraffin.

The paraffin is melted, and while quite hot it is applied with an ordinary paint-brush. It solidifies instantly, forming a thin coating which may be removed later without difficulty. If preferred, the paraffin may be dissolved in benzin, which evaporates rapidly when the solution is applied to exposed surfaces.

Potassium permanganate in solution decomposes all organic matter with which it is brought in contact; it is useful as a deodorant, but not especially as a disinfectant, since it does not attack bacteria more readily than other organic matter.

A solution containing 1 or 2 per cent. of potassium permanganate is useful in the treatment of poisoning with poison ivy (poison oak). The solution is rubbed well into the vesicles to destroy the irritant glucosid on which the action of poison ivy depends. In severe poisoning involving a large part of the hand or forearm, the surface may be immersed in the solution kept as hot as the patient can bear it without too great discomfort. The resulting brown discoloration of the skin may be removed by washing with a dilute solution of oxalic acid.

Bland oils and salves should not be used, because they tend to spread the irritant substance. If large blisters form, they should be opened, and the escaping fluid collected on gauze or in an absorbent powder such as sodium bicarbonate. Scrubbing small affected areas with a stiff hand brush, using soap and running hot water, will suffice to remove much of the irritant from the ruptured vesicles, after which a paste made of soap, or a pad of gauze moistened with an alkaline solution or a dilute solution of lead subacetate, may be applied to the affected skin.

Mercuric chlorid is one of the most powerful disinfectants which we possess, but its action is greatly interfered with by organic matter. It attacks metals, and hence it cannot be used for the sterilization of surgical instruments. It may be used for sterilizing the water which has been used to bathe a patient suffering from an infectious disease, and to sterilize the urine, or even the feces, provided these are nearly

liquid and small masses are disintegrated, but it is not so useful for the latter purpose as a strong mixture of lime and water. A solution containing one part of mercuric chlorid to ten thousand parts of water is rapidly fatal to many spores and all non-spore forms of bacteria. The intensity of the action is of course increased with higher temperatures.

The extraordinary toxicity of mercuric chlorid is one of the greatest disadvantages in its use.

HYDROGEN PEROXID

The official solution of hydrogen dioxid has been freely used and widely abused as a germicide and disinfectant. In the presence of pus or other organic matter it is decomposed with brisk evolution of oxygen. This effervescence is of advantage in its use as a detergent either in connection with open wounds or ulcers, exposed mucous surfaces or as a wash for the mouth and teeth. It is obviously unsuited for injection, into sinuses or subcutaneously, as the gas resulting from its decomposition tends to destroy tissues and spread infection. Hydrogen peroxid applied to bleeding wounds acts as a styptic by coagulating albumin, and has come to be a popular household remedy.

Many of the widely advertised antiseptics are wholly useless as disinfectants, and no one should depend on the directions which accompany these for preventing the spread of contagious diseases. The so-called chlorids, such as Platt's, may have some value as deodorants, but they cannot be used for disinfecting rooms and fabrics.

MATERIA MEDICA

Iodum.—Iodin, U. S. P.

Iodin occurs as heavy bluish-black, friable crystals or masses having a distinctive odor and a sharp and acrid taste. It is quite volatile and is very slightly soluble (1:5,000) in water, but soluble (1:10) in alcohol. It is also soluble in solutions of iodids; it is most frequently applied in the form of:

Tinctura Iodi.—Tincture of Iodin, U. S. P.

Each 100 c.c. contains 7 gm. iodine and 5 gm. potassium iodide dissolved in alcohol.

Iodoformum.—Iodoform, U. S. P.

Iodoform, triiodomethane (CHI_3), occurs as a fine lemon-yellow powder or in lustrous crystals having a peculiar very penetrating, persistent odor and an unpleasant slightly sweetish and iodine-like taste. It is readily decomposed by air and light, and should be kept in well-stoppered bottles in a cool and dark place.

Calx.—Lime, Calcium Oxide, U. S. P.

The official preparation (CaO) is directed to be made by calcining white marble, or the purest variety of native calcium carbonate. For use as a disinfectant, however, the ordinary commercial lime, also known as quicklime, will suffice.

Calx Chlorinata.—Chlorinated Lime, Chlorinated Calcium Oxide, U. S. P.

A compound resulting from the action of chlorine on calcium hydroxide. The official preparation is required to contain not less than 30 per cent. of available chlorine. It is often improperly called chloride of lime. Chlorinated lime occurs as a white or grayish-white, granular powder, having a chlorine-like odor and a repulsive saline taste. It gradually decomposes on exposure to air. It should be kept in well-closed vessels in a cool and dry place. As a disinfectant it is frequently used in the form of:

Liquor Sodae Chlorinatae.—Solution of Chlorinated Soda, U. S. P.—Labarraque's Solution.

An aqueous solution of sodium hypochlorite and sodium chloride, containing at least 2.4 per cent. by weight of available chlorine. It is made by decomposing a solution of chlorinated lime with sodium carbonate and removing the insoluble calcium carbonate formed. A corresponding solution of potash has been used under the popular title "Javelle's solution," but it has no evident advantages over the solution of chlorinated soda.

Liquor Formaldehydi.—Solution of Formaldehyde, U. S. P.

A solution of formic aldehyd, which is also marketed under various trade names and is frequently referred to as "formalin." It should contain not less than 37 per cent. by weight of absolute formaldehyd (HCOH), an oxidation product of methyl alcohol. It occurs as a clear colorless liquid, having a pungent odor and caustic taste. Its vapor acts as an irritant on the mucous membrane. Formaldehyd polymerizes readily with the formation of:

Paraformaldehydum.—Paraformaldehyd, N. N. R.

Solid paraformaldehyd, tri-oxyethylene (CH_2O)_x, which occurs as a white crystalline or amorphous powder or friable mass, odorless at ordinary temperature, but having a pungent odor on heating. It is used chiefly to generate formaldehyd, by heating, for disinfection or for inhalations.

Ferri Sulphas.—Ferrous Sulphate, U. S. P.

Sulphate of iron (FeSO_4), commonly known as copperas, occurs as pale, bluish-green crystals without odor, having a saline styptic taste. It is effervescent in air, and on exposure to moist air the crystals rapidly oxidize and become coated with brownish-yellow basic ferric sulphate.

Sulphur.—Sulphur, U. S. P.

For use as a disinfectant, the ordinary commercial sublimed sulphur either in the form of powder or masses is used.

Potassii Permanganas.—Potassium Permanganate, U. S. P.

Potassium permanganate (KMnO_4) occurs as slender prisms, of a dark purple color, almost opaque by transmitted light and of a blue metallic luster by reflected light, odorless, having a taste at first sweet but afterward disagreeable and astringent. It is soluble (1:15) in water, and decomposes when brought into contact with alcohol, glycerin or other easily oxidizable organic solvents.

Hydrargyri Chloridum Corrosivum.—Corrosive Mercuric Chlorid, U. S. P.—Corrosive Sublimate.

Mercuric chlorid (HgCl_2) occurs in the form of heavy colorless crystals or a heavy white powder hav-

ing an acrid and persistent taste. It is very slowly soluble (1:13) in water and freely soluble (1:3) in alcohol. Ammonium chlorid, sodium chlorid, tartaric acid and citric acid increase its solubility in water. Of the chlorids, the ammonium chlorid is more generally used in this country (probably through mere force of habit), though the sodium chlorid is acknowledged to be more desirable in that it yields a solution that is more permanent.

Aqua Hydrogenii Dioxid.—Solution of Hydrogen Dioxid, U. S. P.—Solution of Hydrogen Peroxid.

The official solution of hydrogen peroxid (H_2O_2) contains approximately 3 per cent., corresponding to 10 volumes of available oxygen. It occurs as a colorless liquid without odor but having a slightly acidulous taste and producing a peculiar sensation and thick froth when taken into the mouth.

Solution of hydrogen dioxid is frequently used as a constituent of mouth-washes, of which the following is a type:

Potassium chlorate	5 parts
Water	100 parts
Hydrogen peroxid	100 parts

Mix, dilute with equal parts of water, and use as a mouth-wash.

VOLATILE OILS

Spices and related aromatic substances have been used as preservatives from time immemorial, but it is only recently that any experiments have been made to determine the relative antiseptic and disinfectant activity of essential oils and their constituents.

Martindale⁶ found that a few of the essential oils compare well with thymol and other phenols in antiseptic activity, though most of them are much weaker.

Oil of turpentine has had an especial vogue as an antiseptic in surgery, but most of the volatile oils have come to occupy a subordinate place among the disinfectants and antiseptics, except for a few special indications, such as that of sandalwood oil in gonorrhea.

The following volatile oils (in addition to those mentioned among the urinary antiseptics) are included in "Useful Drugs."

6. Martindale: Perf. Ess. Oil Rec., 1910, i, 266.

Oleum Cinnamomi.—Oil of Cinnamon, U. S. P.—Oil of Cassia.

A volatile oil distilled from cassia cinnamon and containing not less than 75 per cent., by volume, of cinnamic aldehyd. It occurs as a yellowish or brownish liquid, having the characteristic odor of cinnamon and a sweetish spicy and burning taste. It is only slightly soluble in water, but is soluble in alcohol.

Oleum Carophylli.—Oil of Cloves, U. S. P.

A volatile oil distilled from cloves and containing not less than 80 per cent., by volume, of eugenol. It occurs as a pale to dark yellow liquid having a strongly aromatic odor of cloves and a pungent spicy taste. It is only slightly soluble in water, but is miscible in all proportions with alcohol.

Oleum Eucalypti.—Oil of Eucalyptus, U. S. P.

A volatile oil distilled from the leaves of eucalyptus and containing not less than 50 per cent., by volume, of cineol (eucalyptol). It occurs as a colorless or pale yellow liquid having a somewhat camphoraceous odor and a pungent, spicy, cooling taste. The active ingredient, cineol, is also official as:

Eucalyptol.—Eucalyptol, U. S. P.

An organic oxid ($C_{10}H_{18}O$) obtained from the oil of eucalyptus, or other sources. It occurs as a colorless liquid having a characteristic aromatic and distinctly camphoraceous odor and a pungent, spicy, cooling taste. It is practically insoluble in water, but is miscible in all proportions with alcohol.

Oleum Terebinthinae.—Oil of Turpentine, U. S. P.

A volatile oil recently distilled from turpentine. Its physical properties are so well known that they hardly require description.

BORIC ACID AND BORAX

Boric acid is weakly antiseptic, but hardly at all destructive to the more common bacteria, though it destroys certain molds readily and it is especially useful for the destruction of *Oidium albicans*, the parasite which produces the condition known as thrush.

It is soothing when applied to inflamed mucous membranes in the form of solution or dusting-powder.

but the continued use of even small amounts internally gives rise to gastro-intestinal irritation.

Daily doses of as much as 1 gm. (15 grains) increase the combustion of fats and interfere with their utilization as food, and loss of body weight has been observed after the use of boric acid for a few days.

Borax, or sodium borate, is even less actively antiseptic than boric acid; hence such large amounts are required when it is used as a food preservative that they are almost certain to cause some disturbance if taken continuously in the more commonly used foods, such as milk and butter, especially when the elimination—slow at all times—is interfered with as in nephritis, leading to accumulation of the poison in the body.

Even moderate amounts may induce nephritis, thus setting up a vicious circle of slow elimination and increasing nephritis. Very large doses (such, however, as would not be taken in the form of food preservative) cause gastro-enteritis, disturbances of vision, fatty degeneration of various organs and collapse.

Borax interferes with the coagulation of casein, thereby retarding its digestion; hence its use as a preservative of milk is to be especially condemned.

It is sometimes urged in favor of the use of borax as a food preservative that fish and other perishable foods decompose more readily without its use and give rise to poisoning. Even though it does prevent the decomposition of certain foodstuffs, this does not justify its general use, because it is certainly injurious when used too freely.

Boric acid is commonly used in from 2 to 4 per cent. solution for washing the bladder in cystitis, as a wash in conjunctivitis and in catarrhal conditions of other mucous membranes. It was formerly used freely for washing the rectum and other organs, and large amounts were frequently left in the organ to act as an antiseptic; but severe, and even fatal, poisoning has resulted from this practice in a number of cases.

Boric acid is frequently used in a combination with starch, talcum or other diluent, as a dusting-powder on inflamed surfaces.

Solution of borax is used as a mild antiseptic and astringent eye-wash, and as a gargle and mouth-wash. It may be prescribed somewhat as follows as an eye-wash:

	gm. or c.c.	
R Sodii boratis	0 5	gr. viii
Aquae camphorae	10 0	flʒ iss
Aquae q. s. ad.....	30 0	flʒ i
M.		

A stronger solution may be used as a gargle, or as a wash in pruritus, in which case a small amount of glycerin may be added.

Boric acid has been used internally in cystitis, but with the introduction of better urinary antiseptics, such as hexamethylenamin, its use in that way has been discontinued. There are no clear indications for the internal administration of either boric acid or borax.

MATERIA MEDICA

Acidum Boricum.—Boric Acid, U. S. P.

The official substance should contain not less than 99.8 per cent. of H_3BO_3 . It occurs as transparent colorless scales or a white, unctuous, very fine powder. It is odorless, has a faintly bitter taste and is slowly soluble (1:18) in water and soluble (1:15) in alcohol. Of the preparations of boric acid that are quite widely used, we have:

Glyceritum Boroglycerini. — Glycerite of Boroglycerin, U. S. P.

A glycerin solution containing approximately 30 per cent. of boric acid. It is more readily soluble in water than is boric acid itself, and is also used as a local application to inflamed mucous surfaces.

Unguentum Acidi Borici.—Ointment of Boric Acid, U. S. P.

A 10 per cent. mixture of boric acid with white petrolatum and paraffin used as a protective ointment.

Sodii Boras.—Sodium Borate, U. S. P.

This preparation, popularly known as borax, is more properly designated sodium tetraborate or sodium pyroborate. It should contain in the uneffloresced condition not less than 99 per cent. of $Na_2B_4O_7 + 10H_2O$.

It occurs as colorless, transparent crystals or a white powder, odorless and having a sweetish, alkaline taste. It is soluble (1:17) in water and practically insoluble in alcohol, but very soluble (1:1) in glycerin by the aid of heat. Sodium borate is incompatible with mineral salts, with mucilage of acacia and with the soluble salts of most alkaloids.

Carbo Ligni.—Charcoal, U. S. P.

Charcoal, prepared from soft wood and finely powdered, is sometimes applied to fetid ulcers as a deodorant. It acts by absorbing putrefactive gases and condensing them on its surfaces. Since charcoal is extremely porous, the surfaces available for condensing the gases are more extensive than would at first appear.

It has been used internally with the object of absorbing gases resulting from fermentation, but it is almost devoid of absorbing power when it has become saturated with liquid.

It is sometimes administered in capsules or cachets in order to determine the length of time required for it to pass through the alimentary canal. It is not absorbed, and its appearance in the blackened feces is easily detected.

DISINFECTANTS USED IN SKIN DISEASES

The substances considered under this heading do not constitute a well-defined therapeutic or pharmacologic group, but they are conveniently considered together.

Balsam of Peru¹² consists of a mixture of oils and resins with somewhat more than 50 per cent. of cinnamein (benzyl ester of cinnamic acid) and about 10 per cent. of free cinnamic acid.

Balsam of Peru is absorbed to some extent after its external application, and severe temporary albuminuria frequently follows its free application in the treatment of scabies. In the absence of albuminuria, the

11. It is obviously impossible to discuss the drugs of this group with their therapeutic applications comprehensively, for the treatment of skin diseases constitutes a separate branch of medicine.

12. The term "balsam" has been applied to various substances that are used externally, but the pharmacopeia limits the term to oleoresins that contain aromatic acids, such as benzoic and cinnamic.

urine may contain resin after the use of one of these oleoresins, such as copaiba and balsam of Peru, and this resin may be precipitated by the addition of acid, giving rise to the mistaken diagnosis of albuminuria. The precipitated resin may be dissolved in an excess of alcohol.

Tar contains numerous antiseptic substances, including phenol and the cresols, but the less toxic members of the group (creosol and guaiacol) are more abundant than phenol, and tar is therefore actively disinfectant without being so toxic as phenol.

It is absorbed slowly through the skin, which it irritates only slightly.

Resorcinol, or dioxy-benzol, differs chemically from phenol in that it has two OH groups instead of one. Its systemic actions resemble those of phenol, but it is somewhat less caustic and toxic than the latter.

Chrysarobin is closely related to chrysaphanic acid, a constituent of several of the purgative drugs of the anthracene group. Chrysarobin is too actively irritant to be used internally. When swallowed, it causes nausea, vomiting and diarrhea. It is absorbed slowly from the skin, and is excreted through the kidneys, which it irritates, causing albuminuria in some cases. A part of the chrysarobin is oxidized to chrysophanic acid during its passage through the body.

It is actively irritant to the skin, causing itching and redness and sometimes pustulation.

Chrysarobin stains the skin, nails and clothing, and this constitutes a serious objection to its use. The stains may be removed by washing with a weak solution of sodium hydroxid or a solution of chlorinated soda or chlorinated lime.

When sulphur is applied to the skin, it is converted in part into hydrogen sulphid, which is irritant. It is especially destructive to the parasite that infests the skin and causes itch. The internal use of sulphur is mentioned in connection with its use as an evacuant.

Sodium sulphite and thiosulphate are antiseptic and are commonly used externally in the treatment of parasitic skin diseases. Either of these salts may be used in a 10 per cent solution as a local application in

scabies and favus, and as a mouth wash in aphthous stomatitis, mucous patches and ulcers of the tonsils. The thiosulphate is sometimes used for ringworm.

They are sometimes used internally, but there is no clear indication for their use in that way.

The thiosulphate is used for the removal of stains on the skin caused by iodine and silver nitrate. It is also widely used in photography.

THERAPEUTIC USES

Balsam of Peru has been used subcutaneously in pulmonary tuberculosis with a view to its causing inflammation with cicatrization in the diseased areas. It has not proved satisfactory, but sodium cinnamate is still used intravenously for this purpose occasionally. Balsam of Peru seems to be of some value in the treatment of lupus, scabies and other parasitic skin diseases. It may be painted over the skin on retiring and washed off the next morning, or it may be used in the form of an ointment containing 1 part each of balsam of Peru, green soap, sulphur and chalk, and 25 parts of petrolatum.

Syrup of tar is often used in cough mixtures. A solution or ointment containing from 2 to 4 per cent. of tar may be used in the acute inflammation of pruritus, the strength of the application being increased gradually if necessary. Tar is sometimes applied without dilution in the chronic forms. The official ointment may be used without dilution in ringworm and in psoriasis, the weaker applications in eczema.

Resorcinol, or resorcin, is rarely used internally because of its toxicity, but it has been used in doses 0.3 gm. (5 grains) to stop gastric fermentation. It is sometimes used in 10 per cent. solution against dandruff, and a solution or ointment may be used for pruritus.

Chrysarobin is used chiefly in the treatment of psoriasis, but it should not be applied to the face and head, because it irritates the mouth, eyes and nose. It is commonly used in the form of an ointment containing from 2 to 20 per cent. of the drug, but the *weaker* is said to act as well as the stronger without

causing dermatitis in many cases. It has been suggested that it acts by withdrawing oxygen from the skin.

Sulphur is commonly used in the form of an ointment as a parasiticide in the treatment of scabies (itch). As this troublesome parasite burrows under the skin, it is necessary to use an ointment that is soft enough to be rubbed well into the skin or is slightly alkaline so as to soften or modify the outer horny layers of the skin. The following may be used as a type formula for the latter form of ointment:

Sublimed sulphur.....	20 parts
Precipitated calcium carbonate.....	15 parts
Soft soap	35 parts
Lard	35 parts

An ointment formerly much used in England in the treatment of scabies is made as follows:

Precipitated sulphur	2 parts
Potassium carbonate	1 part
Lard	8 parts
Mix and make into an ointment.	

The official diluted mercurial ointment (33 per cent.) is very commonly used for the destruction of body lice. It is interesting to note that the louse that transmits typhus fever remains attached to the inner surface of the clothing and not to the human body. Ointment of ammoniated mercury is used in the treatment of psoriasis.

MATERIA MEDICA

Balsamum Peruvianum.—Balsam of Peru, U. S. P., occurs as a dark brown liquid having an agreeable odor and a bitter, acrid taste. It is freely soluble (1 : 1) in alcohol and in chloroform, but only partially soluble in ether and in petroleum benzin. Water dissolves out traces of the contained cinnamic acid.

Pix Liquida.—Tar, U. S. P. This substance, also known as wood tar or Stockholm tar, is obtained by the destructive distillation of pine wood. It occurs as a viscid, blackish-brown, semiliquid, having an empyreumatic odor and a sharp, terebinthinate taste. Tar is miscible with alcohol and the fixed and volatile

oils, and should not be confounded with coal tar, a by-product in the destructive distillation of bituminous coal.

Unguentum Picis Liquidæ.—Tar Ointment, U. S. P. A mixture of tar (50), yellow wax (15) and lard (35).

Resorcinol.—Resorcinol, U. S. P. A dihydric phenol that occurs as white or nearly white, needle-shaped crystals, having a faint, characteristic odor and a sweetish followed by a bitter taste. It is very soluble (1:0.5) in both water and alcohol.

Chrysarobinum.—Chrysarobin, U. S. P. A mixture of substances extracted from Goa powder. It occurs as a pale orange-yellow crystalline powder, practically odorless and tasteless, but irritating to the mucous membrane. It is very slightly soluble (1:1,812) in water, and rather more soluble (1:308) in alcohol. It is freely soluble in dilute or in concentrated solutions of the alkaline hydroxids.

Unguentum Chrysarobini.—Chrysarobin Ointment, U. S. P., represents a solution of about 5 per cent. of chrysarobin in benzoinated lard.

Sulphur in its several forms will be discussed in connection with its use as an evacuant, but the only preparation of direct value in the treatment of skin diseases is:

Unguentum Sulphuris.—Sulphur ointment, U. S. P. A mixture of washed sulphur (15) with benzoinated lard (85). Some practitioners prefer to use the precipitated sulphur, which is somewhat more finely divided and therefore more active.

Mercurial ointment is official in two forms:

Unguentum Hydrargyri.—Mercurial Ointment, U. S. P. A mixture of mercury (50) with prepared suet and benzoinated lard (to make 100).

Unguentum Hydrargyri Dilutum.—Blue Ointment, U. S. P. A mixture of mercurial ointment (67) with petrolatum (33).

Hydrargyrum Ammoniatum.—Ammoniated Mercury, U. S. P., popularly known as white precipitate, represents about 80 per cent. of metallic mercury in

the form of the insoluble mercuric-ammonium chlorid. It is generally used in the form of:

Unguentum Hydrargyri Ammoniaci.—Ointment of Ammoniated Mercury, U. S. P.—A mixture of ammoniated mercury with white petrolatum and hydrous wool fat.

Sodii Sulphis.—Sodium Sulphite, U. S. P., $\text{Na}_2\text{SO}_3 \cdot 7\text{H}_2\text{O}$. It occurs as colorless, transparent crystals. It is freely soluble (1:2) in water, but practically insoluble in alcohol. Mineral acids decompose it with the liberation of the irritant gas, sulphur dioxid.

Sodii Thiosulphas.—Sodium Thiosulphate, U. S. P. (Sodium Hyposulphite, U. S. P. 1890). $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$. It occurs as colorless transparent crystals that are very soluble in water (1:0.5), but practically insoluble in alcohol. It is incompatible with acids, iodine and chlorine.

CHAPTER V.—DRUGS WHICH STIMULATE SYMPATHETIC ENDINGS

EPINEPHRIN

Oliver and Schaefer investigated the actions of extract of the suprarenal gland previous to the isolation of an active principle by Abel in 1897. This active principle has been prepared by many workers, by whom it has been given different names, including "epinephrin," "suprarenalin," "supracapsulin," "adrenin" and "adrenalin," the last being the commercial name by which it is commonly known. The synthetic preparation has likewise received a number of names, including "homorenon" and "l-suprarenin synthetic."

The epinephrin obtained from the gland is levorotary, but the artificial is either levorotary or dextrorotary, or it may consist of a mixture of these two. Levorotary epinephrin is of uniform activity, so long as it has not undergone decomposition, to which it is prone, whether it is derived from the gland or prepared artificially. The market supply of artificial epinephrin is levorotary.

Dextrorotary epinephrin is only about one-fifteenth as active as the levorotary, according to Cushny. Mixtures of the two forms are of variable activity.

Epinephrin stimulates the sympathetic myoneural junctions in muscles. Elliott has stated it as a law that the action of epinephrin on these connections between any given nerve and its muscle proves that the innervation is of the sympathetic system—in other words, that epinephrin acts only on the endings of the sympathetic. It is also true that it acts on all of these, with possibly one exception, and we shall see that the innervation of the sweat-glands in the skin, which is always attributed to the sympathetic, behaves toward many drugs, including atropin and pilocarpin, as though it belonged to the parasympathetic system. *Epinephrin* does not act on them.

This conception of the actions of epinephrin simplifies its pharmacologic study, for the actions of epinephrin on any structure of the body are simply those of stimulation of the sympathetic.

When this stimulation results in inhibition, as it does in the non-pregnant uterus of some animals, then epinephrin also causes inhibition; but if stimulation of the nerve causes motor effects, as it usually does in the pregnant uterus, then epinephrin also causes motor effects. A given dose of epinephrin, however, varies widely in the intensity of its action in different organs, and these differences must be understood in order that epinephrin may be used therapeutically.

When it is injected intravenously no pronounced action is observed on the higher parts of the central nervous system, and the effects on the medullary centers are mainly secondary to the rise of blood-pressure. For example, the heart is accelerated at once after an intravenous injection, because of the stimulation of the sympathetic myoneural junctions, or endings, as we shall call them for convenience, in the heart; following this the vagus center is stimulated by the higher blood-pressure, and the heart is slowed. The action on the respiratory center is somewhat peculiar, resulting in an interruption of respiration, followed by a period during which the rate and the depth are increased, interruption and augmentation alternating.

The most prominent effect which follows the intravenous injection of epinephrin is the sudden high rise of blood-pressure, which is comparable to that seen after the intravenous injection of convulsive doses of strychnin. This is due to the increased heart-rate and strength of beat and to the constrictor action on the vessels. In practice this sudden rise of pressure is avoided by injecting very dilute solutions slowly. The heart soon becomes much slower and the blood-pressure falls below normal and then returns to its original level. The cause of the extreme brevity of the action of epinephrin on the vessels has been the subject of much debate. Apparently the action lasts only so long as the drug is actually in course of penetration into the endings, and when equilibrium is reached between

the concentration of the drug in the blood and that in the nerve-endings the action ceases. It has been shown that the musculature of the vessel walls does not become fatigued so readily, for the high blood-pressure can be maintained almost indefinitely by the slow, continuous injection, and the destruction of the drug in the blood is not sufficiently rapid to account for the fleeting nature of the action.

Epinephrin does not affect the vessels of all areas equally, some being much less under the control of the sympathetic than others, and the cerebral, pulmonary and coronary arteries react so slightly that it has been denied frequently that the drug has any influence over them. The larger trunks of the pulmonary artery do, however, show marked constriction, the primary branches less and the smaller twigs little or none.

The coronary arteries often behave in a manner opposite to that of the vessels of other large areas. It has been found that exceedingly small amounts of epinephrin—much less than those required to increase the general blood-pressure—cause constriction of the coronaries; with moderate amounts, such as cause a rise in the general blood-pressure, the coronaries show at most a fleeting constriction and a rapidly following dilatation.

The necessity for the difference in the behavior of the coronary arteries and those of the general arterial system is readily apparent. When the general blood-pressure rises, the heart must perform more work, which would be impossible if its supply of blood were diminished essentially, for it has been shown conclusively that the functional capacity of the heart and its blood-supply are very closely related. If the rise of blood-pressure following the injection of epinephrin were attended with constriction of the coronaries of sufficient degree to interfere seriously with its supplying blood to the heart, the latter would be exhausted rapidly. This discussion bears on the action of other drugs which affect the heart and the general circulation, and it may be accepted as a rule that no drug which increases the work of the heart can interfere seriously with its blood-supply if the condition of the

heart improves under its use. Mention of this will be made when digitalis is under discussion. Epinephrin stimulates the vasodilators as well as the vasoconstrictors, in the general circulation, but the action on the latter usually predominates, at least for a time.

When the vasoconstrictor nerves are paralyzed by apocodein or ergotoxin, the administration of epinephrin results in stimulation of the dilators from the beginning, and the primary action of epinephrin then causes a fall of blood-pressure.

This secondary dilatation which follows the constrictor effect of epinephrin may become annoying at times. If epinephrin is heated to a temperature of 120 C. (248 F.), the constrictor action is lost while the dilator is maintained, and a similar change may apparently take place when the solution has been kept open for a time. One of us (Hatcher) has seen a specimen of which even small doses caused a rapid fall in the blood-pressure without any preliminary rise. The specimen had been kept on hand, but unopened, for some weeks.

Epinephrin causes constriction of the vessels of the mucous membrane to which the solution is applied, resulting in relief in various inflammatory conditions, but the frequent application with alternate constriction and dilatation may ultimately give rise to hypertrophy of the mucous membrane, with a chronic inflammatory condition. Secondary hemorrhage may follow the use of epinephrin in surgical operations when the vascular dilatation succeeds the constriction, and a fall of blood-pressure may succeed its use in shock of minor importance. Such hemorrhage frequently occurs from four to six hours after the use of epinephrin in operations on the turbinate bone, and the patient should be kept under the supervision of a surgeon after such operations.

The pupil behaves differently to epinephrin in different animals; in man epinephrin has little effect under normal conditions, but in exophthalmic goiter the sympathetic nerve to the eye shares with other sympathetic nerves an increased susceptibility to stimulation; epinephrin then causes dilatation of the

pupil. Hence this reaction may become of some diagnostic importance in cases of suspected Graves' disease. It is possible that the reason for the increased effect of epinephrin in exophthalmic goiter is that the blood then contains more than the normal amount of epinephrin, and that the sympathetic is kept under more active control by it.

A similar mydriatic action occurs with epinephrin in pancreatic diabetes.

The application of epinephrin to the eye causes constriction of the vessels of the conjunctiva and increases the mydriatic action of cocain. We have already seen that cocain increases the constrictor action of epinephrin.

The uterus behaves differently toward stimulation of the sympathetic in different animals, and in some it responds with contraction in the later stages of pregnancy, but not in the virgin. The human uterus during pregnancy responds with contraction to sympathetic stimulation; consequently it responds to epinephrin with contraction, and so actively that even the subcutaneous injection of epinephrin, which does not affect the blood-pressure to an important degree, causes uterine contractions. This is of therapeutic importance, in that it permits of the use of epinephrin after delivery of the placenta in securing firm contraction of the uterus without increasing the blood-pressure. Increase of blood-pressure is undesirable, since the object is to prevent post-partum hemorrhage.

Epinephrin acts on the heart in various ways. It accelerates the rate and increases the energy by stimulating the sympathetic. This and the vasoconstriction induced cause an increase of blood-pressure which acts on the vagus center, producing a secondary slowing of the rate. When the vasoconstriction ceases, as it does in two or three minutes after the injection is completed, the blood-pressure falls, and the heart is again accelerated by the stimulation of the sympathetic, or it may be that the increased rate is due to the lowered blood-pressure, since the heart normally responds to lowered blood-pressure by increase in rate.

So remarkable is the action of epinephrin on the heart that the latter may sometimes be restored to normal rhythm after having been stopped by ether. On the other hand, the rapid intravenous injection of a large dose is capable of causing a normal heart to stop promptly. Intravenous injections of epinephrin must be made with extreme caution. It will be recalled that other drugs are also very much more active by intravenous injection than by other modes of administration, and while this method is essential in some cases, it must be looked on as suitable only for emergencies.

The action of epinephrin on the intestine is that of stimulation of the sympathetic, but the action is too brief to admit of its therapeutic application.

Epinephrin is one of the few alkaloids in the *materia medica* which are not absorbed from the gastro-intestinal canal with such rapidity as to induce any appreciable effect. When injected subcutaneously it causes an unimportant rise in blood-pressure, but, as previously stated, enough of it is absorbed to cause tonic contraction of the uterus when it is administered after the delivery of the placenta. Intramuscular injections are followed by a greater rise of blood-pressure than are subcutaneous injections, but not nearly so great as that following the intravenous injection. The intense constriction of the vessels in the immediate region of the injection retards the absorption.

Epinephrin is absorbed from the mucous membrane of the nose, throat, mouth, urethra, vagina and rectum.

Epinephrin is destroyed almost immediately in alkaline solution, and it was suggested that the brief action after intravenous injection might be explained by its destruction in the alkaline blood. The blood, however, is now known to be practically neutral in reaction, and epinephrin mixed with blood and allowed to stand twenty-four hours is not totally destroyed, but if oxygen be passed through the blood after the addition of epinephrin, the latter is destroyed rapidly. Epinephrin is also destroyed in the other tissues.

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Many biologic tests have been proposed for estimating the amount of epinephrin in specimens taken from the circulating blood, but most of the reactions which have been proposed are given by other substances; hence they have only a negative value. That is, when the blood fails to respond to these tests, epinephrin may be considered as absent; at least, no more than traces can be present. A recently proposed test of extreme delicacy, which is said to respond only to epinephrin among the substances which one might expect to find in the blood, consists in the perfusion of the vessels of an isolated limb of the frog with the blood to be tested, which is added to Ringer's solution in such dilution that it just causes constriction. One part of epinephrin in 800,000,000 of the perfused fluid can be detected in this way.

Solutions of epinephrin decompose on exposure to light and air, becoming pinkish and later brown in color.

THERAPEUTIC USES

The principal therapeutic indications of epinephrin have been indicated, for nearly all of these depend on its constrictor action. The circulatory effects may be utilized when a rise of blood-pressure is desired; where it is necessary to maintain an increased blood-pressure for some time, resort may be had to slow intravenous injection of a very dilute solution (1:100,000), but there are many difficulties in the way of maintaining the injection for prolonged periods. It should be noted that the administration of epinephrin may result in an increase in a hemorrhage, quite as well as in a decrease. Nature lessens hemorrhage by a fall of blood-pressure not by a rise—the latter occurring in hemorrhage only when the circulation in the nervous centers becomes insufficient to sustain life.

Epinephrin finds its greatest field of usefulness in local applications for constricting the vessels of mucous membranes, and in bleeding areas. It is added to solutions of cocain and other local anesthetics to delay absorption and thus prolong and intensify the anesthetic action.

Applications of epinephrin to the nasal mucous membrane during an attack of hay fever or acute catarrh cause immediate shrinking of the inflamed tissues, affording prompt relief. The action is brief, but if the patient remains quiet in a warm room the relief is much more lasting. As previously stated, dilatation commonly follows the constriction after application to the nasal mucous membrane, and if the drug be repeated too frequently for prolonged periods, chronic inflammation results.

Epinephrin is used in bronchial asthma, but as the cause of this condition is unknown, the mode of action of epinephrin is not understood.

It is sometimes injected subcutaneously—not intravenously—after the delivery of the placenta to induce firm contraction of the uterus, preventing hemorrhage.

Epinephrin has been suggested as an antidote to strychnin, but it increases the action of that alkaloid on the cord and cannot be considered as in any way antidotal, though strychnin is said to be antagonistic to the depressant action of epinephrin. The action of the latter is usually so rapid after fatal doses that little time is available for treatment.

Suprarenal gland is recommended for the treatment of Addison's disease (tuberculous disease of the suprarenal gland), but it is admitted that the results are usually unsatisfactory.

HEMORRHAGE

When hemorrhage results from injury to a vessel which can be tied, the latter treatment is obviously indicated; but when it occurs in an inaccessible region, or results from injury to large areas where capillaries are involved, resort to drugs is often necessary. The most diverse methods have been employed in attempting to stop hemorrhage from inaccessible vessels; but since bleeding has a strong tendency to cease spontaneously owing to the formation of a clot when the pressure falls sufficiently, it is difficult to define the rôle of drugs, and when success attends their use, they are too frequently credited with the result when they have actually done harm, or had no appreciable effect.

The results of experiments with drugs in hemorrhage are contradictory, and it is impossible to state just what value many of these have under different conditions.

Epinephrin stops capillary hemorrhage, but when the constriction has passed, dilation and increased oozing may occur. A laboratory experiment serves to illustrate the natural control of hemorrhage and the effects of the injection of epinephrin during bleeding. If the dog's chest be opened under ether anesthesia, and a section of the chest be removed, there is at first a copious hemorrhage from numerous arteries which are cut across; but with the exposure of the thoracic cavity, there is a sudden fall of blood pressure and the hemorrhage ceases almost completely; if epinephrin, or other vasoconstrictor be injected into a vein, the blood begins to spurt from numerous arteries. This continues until the constriction passes, or until the loss of blood causes a great fall in the pressure.

There is a superficial similarity between the action of heat and that of epinephrin. When a bleeding finger is dipped in water, the bleeding increases temporarily, because the vessels in the finger dilate while the general blood pressure is unaffected, of course; when the finger is removed from the hot water, constriction soon takes place and the retardation of the flow favors the formation of a clot.

It has been said that certain vasoconstrictors lessen hemorrhage by favoring the formation of a clot, after temporarily increasing the bleeding, in the manner described above.

Whether such a drug will do harm or good in a given case depends on factors which cannot always be determined. If the loss of blood has been so great as to have reduced that in the body to the point at which further loss will be fatal, it is obvious that the sudden rise of pressure and the consequent loss of blood may prove fatal promptly; but when the fall of pressure does not suffice to stop the flow or permit of the formation of an effective clot, it may be better to suffer the slight additional loss if clotting will ensue. It can only be said that our knowledge on this point is wholly unsatisfactory, and interference will often



prove disastrous, at a time when one must feel the urgent need of action.

Tannin, ferric salts, including the solution of ferric subsulphate or Monsell's solution, alum and dilute acids, such as vinegar, are among the best of the astringents for local application to stop bleeding by favoring the formation of a clot.

Since the fall in blood pressure is the natural means of favoring clotting, it may be advisable to administer a vasodilator early in severe hemorrhage before the pressure has fallen dangerously low; amyl nitrite, sodium nitrate or nitroglycerin may be used in an emergency.

It would be preferable to lessen the circulation by slowing the heart, if this could be accomplished without causing an increased force of the individual beat, for the stronger impulse tends to dislodge clots, and the mechanism controlling the circulation usually results in stronger beats to compensate for any slowing.

Gelatin has been used to some extent in solution for hypodermic injection to promote the formation of a clot in aneurysm and to arrest hemorrhage. It is sometimes contaminated with the spores of tetanus which are not killed by boiling for a few minutes, and many cases of tetanus have been reported from its injection.

DOSAGE

The dose of epinephrin will obviously depend much on the purpose for which it is employed. It is applied to the nasal mucous membrane in the form of a spray of the 1:1,000 solution for hay fever, catarrh, or to reduce the swelling of the turbinated body. From 0.2 to 0.3 c.c. (3 to 5 drops) of a 1:1,000 solution may be added to a solution of cocain for subcutaneous injection to delay absorption and prolong local anesthesia. Much larger doses are sometimes injected subcutaneously in order to secure bloodless fields of operation. No harm follows unless the dose is excessively large, because of the slow absorption, but when the dose exceeds 0.5 mg. ($\frac{1}{125}$ grain), care must be taken to see that the hypodermic needle does not enter a vein.

When epinephrin is injected intravenously to increase the blood-pressure in shock, a solution of 1:10,000, or even a weaker one, should be used, and this should be injected very slowly, 1 c.c. (15 minims) in five or ten minutes being sufficient to maintain slight rise in the pressure. For capillary hemorrhage a solution of 1:1,000 is used. It is said that little improvement is to be expected in most cases of bleeding from gastric ulcer, because of the dilution to which the epinephrin is subjected in the fluid in the stomach. Epinephrin may be used in far larger doses by the mouth than intravenously, and if it fails to stop the bleeding it will probably do no harm. From 5 to 10 c.c. (from 1 to 2 teaspoonfuls) of a solution 1:10,000 may be used.

For the relief of bronchial asthma 0.6 to 1.0 c.c. (10 to 15 minims) of a solution of 1:1,000 subcutaneously is recommended, or sprayed into the nose at the beginning of the attack, or 1 mg. ($\frac{1}{60}$ grain) may be used in the form of a tablet which is allowed to dissolve in the mouth.

When the heart stops suddenly during the administration of ether or chloroform, it is essential that the beat be restored immediately, for the chambers of the heart are then filled with blood containing the anesthetic, and especially when this occurs with chloroform, the heart is rapidly paralyzed and rendered incapable of contracting again. If epinephrin is injected intravenously in such cases it must traverse the right heart and the pulmonary circulation before it can act on the left ventricle, involving the loss of valuable time. If the injection is made intravenously the heart should be massaged through the chest wall at the same time. Delay is avoided by injecting the solution of epinephrin, 1 c.c. (15 minims) of 1:10,000, directly into the heart by means of a fine hypodermic needle.

MATERIA MEDICA

Epinephrina.—Epinephrin, N. N. R.

This substance, commonly referred to and used as adrenalin, is described as 1,2-dihydroxy-4² methyl-amino ethyl-4¹-ol, benzene. It is the blood-pressure-raising principle of the suprarenal gland, also pro-

duced synthetically. Among the names, other than those already mentioned, that have been applied to epinephrin or epinephrin-like substances are "adneph-rin," "adrenal," "adrenamine," "atrabilin," "chela-frin," "epirenan," "haemostasin," "hemisine," "ischae-min," "paranephrin," "renaglandin," "renastyptin," "renoform," "supranefran," "suprarenin," "supra-renadin," "1-suprarenalin," "suprarenaden" and "suprenalin."

The several mixtures of epinephrin with cocain, eucain and other substances have also been given special names, so that the nomenclature of this article and its simple mixtures would probably total at least one hundred titles.

Epinephrin, as such, occurs in commerce as a finely crystalline white or yellowish white powder, odorless, having a slight bitter taste. The free base is practically insoluble in water and the product is usually dispensed in the form of an aqueous, usually acid, solution, 1:1,000, of one of its salts. Epinephrin is oxidized readily with the development of a red color; and such red, pink or turbid solutions should not be used.

Epinephrin is frequently used in the nose in the form of a spray. For this purpose the commercial 1:1,000 solution may be diluted with 4 parts of water or physiologic solution of sodium chlorid, and if necessary a sufficient amount of cocain hydrochlorid added as in the following formula:

	C.c. or Gm.	
R Solution of epinephrin, 1:1,000	6	fl̄ss
Cocain hydrochlorid.....	0 6	
Distilled water or physiologic solution of sodium chlorid to make.....	30	fl̄i

Epinephrin is sometimes prescribed with an alkali, such as sodium bicarbonate, or with sodium benzoate. The first is evidently incompatible, and the second is hardly less objectionable, for the trace of hydrochloric acid usually present in solutions of epinephrin reacts with the benzoate, liberating benzoic acid, which has little preservative action so far as the epinephrin is concerned.

For use in suppositories epinephrin hydrochlorid is preferable to epinephrin itself because of the greater solubility and consequent activity of the salt. Suppositories of epinephrin may be prescribed by directing that each suppository contain approximately 0.001 gm. ($\frac{1}{65}$ grain) of epinephrin hydrochlorid and a sufficient amount of oil of theobroma to make 1 gm.

PITUITARY

The pituitary body, or hypophysis, consists of two portions, a large anterior lobe, and the posterior, or infundibular, portion. The anterior lobe is glandular in character; it is essential to life; at least, its total removal has usually been followed by the death of the animal, while its partial removal, or injury by disease, results in retarded growth or infantilism in the young, and in obesity and other disturbances of nutrition, the evidence suggesting that it has an internal secretion. Acromegaly and gigantism have been frequently found to be associated with tumor or hypertrophy of the pituitary, and it is believed that the abnormality is related to the change in the anterior portion.

The therapeutic administration of the anterior lobe has given favorable results in the later stages of acromegaly and in the condition known as dystrophia adiposo-genitalis, though it is, of course, contraindicated in the early stages of acromegaly.

The intravenous administration of extracts of the anterior lobe cause no marked physiologic actions on the circulation or respiration, but Cushing and Goetsch have observed some interesting effects on the reproductive organs following the use of the anterior lobe, and histologic changes in it have been observed in hibernating animals.

Despite the fact that this portion of the pituitary body is essential to life, extracts of it appear to be of little, or no, therapeutic importance at present, and the following discussion applies only to the posterior lobe and its preparations.

The posterior, or infundibular, portion (and with this may be included what is called the *pars intermedia*) consists mainly of neuroglia cells and fibers.

It yields to boiling water and other solvents various principles on which its pharmacologic and therapeutic actions depend, but none of these principles is available in pure form. This has resulted in confusion regarding the actions of the extracts of the pituitary.

The intravenous or subcutaneous injection of extract of the pituitary body cause stimulation of plain muscle, especially that of the blood vessels and uterus. This stimulation of the musculature of the vessels causes a moderate, but somewhat prolonged, rise of blood pressure. This rise is seldom as great as that which may be obtained by suitable amounts of epinephrin, and while some observers report that it may persist for as much as half an hour, this is seldom seen after the injection of commercial preparations into dogs, and the blood pressure usually falls below the previous level within five minutes.

Subsequent injections cause diminishing rises if suitable intervals of time are permitted to elapse, but eventually a condition is reached where the injection causes only a fall in pressure.

The rate of the heart beat is slowed, partly due to the direct action on the heart itself, but the contraction is apparently not favorably influenced through this direct action.

The renal vessels dilate while the splanchnic vessels constrict, and this effect has been invoked to explain the well-known diuretic action of pituitary, but there is no reason to doubt that it also acts directly on the renal cells causing an increased secretion, both actions probably being concerned in the diuresis.

The actions of pituitary on the uterus are important, but unfortunately there is a want of exact agreement among investigators on this point, especially among clinical observers. There is no question concerning the capacity of pituitary to stimulate the musculature of the uterus to increased contraction, and it has been shown that the effect is much greater during pregnancy than during the non-pregnant state, but the question of the degree to which it causes tonic contraction of that organ is naturally of the first importance.

The intestinal musculature is also stimulated by pituitary, but, for obvious reasons, this action is of much less importance than that on the uterus. It is used for its uterine effects when a comparatively few active contractions serve to expel the contents, or later, to cause tonic contractions to prevent hemorrhage, but a few extra peristaltic intestinal movements would be of no great value in chronic constipation and tonic contraction of the intestine is, of course, undesired.

We are in especial need of more comprehensive knowledge of the pharmacologic actions of pituitary, especially since the manufacturers of the numerous preparations are most optimistic regarding the therapeutic value of their preparations in a great variety of conditions, in some of which they are certainly useless, if not positively dangerous.

An increased secretion of cerebrospinal fluid, and a temporary increase in the secretion of milk have been observed. The secretion of milk soon falls below the normal, however, and the mammary action appears to be of no therapeutic importance.¹

Various methods have been proposed for standardizing the pituitary preparations, but the most satisfactory consists in comparing the activity with that of pure beta-aminazolyethylamin on the isolated uterus of the virgin guinea-pig. A dilution of 1 part of pituitary extract of good quality in 10,000 is equal in activity to 1 part of pure beta-aminazolyethylamin in a dilution of 20,000,000.

Unfortunately, the various commercial preparations of pituitary vary widely in their activity, and it should be remembered that tests based on the capacity for increasing the blood pressure or the secretion of urine afford no index of the activity on the uterus. Since the therapeutic value of pituitary depends on its uterine action, physicians should demand preparations that have been standardized by comparison with beta-aminazolyethylamin in the manner mentioned.

1. Numerous other effects have been reported as following the injection of pituitary, but many of the results reported lack agreement and they do not call for discussion here. A review of much of the literature may be found in Hygienic Laboratory Bulletin No. 100, November, 1914.

THERAPEUTIC USES

It would be a waste of time to attempt to enumerate all of the conditions in which pituitary has been recommended; rather is it our duty to call attention to some of the therapeutic claims made by manufacturers that have no rational basis, in the present state of our knowledge. For example, one preparation has been recommended "in every individual stage of labor," but careful observers are in agreement that it should not be used before the os has dilated or become dilatable. It has been extolled in paralytic distention of the intestine, but it is not dependable in that condition. It probably has little, or no, value in shock.

Quigley (*Jour. Am. Med. Assn.*, 1915, 64, 1122) states that the ideal conditions for the use of pituitary (note that he does not say that pituitary is ideal for the condition) is uterine inertia occurring during the second stage of labor, that is, when the os is fully dilated or dilatable, with a presenting part that is engaged or that can be made to engage, and in the absence of any obstruction on the part of the passage or the passenger.

He states that its action in post-partum hemorrhage is more prompt than that of ergot but not so lasting.

Quigley and others lay especial stress on the existence of any obstruction, such as contracted pelvis or an occiput posterior stationary at the brim, as a contraindication for the use of pituitary.

Rupture of the uterus has followed the use of pituitary in several cases where obstructions to rapid delivery existed.

DOSAGE

As much as 4 c.c. (60 minims) of pituitary extract was used by some of the observers in the earlier stages of pituitary therapy, but there is no apparent reason for the employment of such doses; when a moderate amount proves ineffectual in causing increased uterine contractions it may be repeated once, but if this has no effect it indicates that the drug is unsuitable for that case.

In the absence of uniformity of activity in the commercial preparations of pituitary, and since there is no official preparation of it, no exact dose can be given,

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but 0.5 c.c. (8 minims) is the average dose of an extract of which a dilution of 1:10,000 is equal in uterine activity to a dilution of beta-iminazolyethamin of 1:20,000,000.

Solutions of pituitary extract undergo decomposition on exposure to the air and only sealed ampules containing one or two doses should be used.

MATERIA MEDICA

There are many preparations of pituitary. Pituitary Liquid, Armour, and Solution Pituitary Extract, Mulford, supplied in 1 c.c. ampules, are described in New and Nonofficial Remedies.

Desiccated Pituitary Substance (Anterior Lobe), N. N. R., occurs as a light grayish yellow powder having a slight, peculiar odor. This is the preparation that has been used in the later stages of acromegaly and in certain cases of obesity. It is given in doses of from 0.05 to 0.20 gm. (1 to 4 grains) in powder or in capsules.

Desiccated Pituitary Substance (Posterior Lobe), N. N. R., like the preceding, is a light grayish yellow powder with a slight, peculiar odor and is partly soluble in water. It may be given by mouth in doses of from 0.5 to 0.20 gm. (1 to 4 grains), but this method of administration is said to be less effective than the parenteral introduction of aqueous extracts which may be made extemporaneously by extracting the soluble portions of (0.5 gm.) the ground substance with (10 c.c.) distilled water by boiling for ten minutes or more, allowing to cool and using the supernatant clear liquid. It should be remembered of course that the preparation used should be active and of standard quality and that proper precautions be used in making the solution to prevent bacterial contamination.

ERGOT

Various grains are invaded by a fungus known as ergot; that growing on rye and replacing its grain is the official ergot. In damp seasons this fungus may constitute as much as 10 per cent. of the flour made from the rye, and the bread made from such flour is

poisonous, giving rise to a condition known as ergotism. The symptoms are of two general types, in one of which convulsions are the predominant feature, and in the other gangrene. These types are not sharply separated, and both are usually seen in epidemics of ergotism. Such epidemics are now uncommon, but they still occur occasionally.

Premature delivery and abortion were frequently observed during epidemics of ergotism, and this probably led to the use of ergot in obstetrics. Ergotism, however, does not always prevent the normal progress of labor.

The marked differences observed in the general types of poisoning suggest strongly that ergot differs widely in its constituents at different times, and this has been shown to be the case. Ergot has proved an unsatisfactory drug at best for the clinician, while its chemistry has presented many difficulties for the investigator.

It has been claimed on many occasions that the active principle of ergot had been discovered, but experience has shown invariably that the supposed active principle represented at most a part of the activities of the drug, and often an insignificant part.

This much is certain, that ergot contains a number of active principles, some of them present in minute quantities, but having extraordinary activity, and there are at least four constituents which deserve mention. These are ergotoxin and ergotinin, two alkaloids which are closely related, and two principles commonly considered as putrefactive principles, because they are present in putrefying meat; these are tyramin, or hydroxy-phenyl-ethyl amin and histamin, or beta-iminazolyl-ethyl-amin.

Ergotoxin, an extremely active alkaloid, is the hydrate of ergotinin, which is inactive, but which is probably changed into ergotoxin under conditions which are not very well understood. Ergotinin has been known since 1875; ergotoxin, only recently discovered in pure form, constitutes the active portion of various substances which have been isolated in greater

or less degree of purity by various investigators and given different names.

Ergotoxin stimulates those sympathetic endings which have motor functions, and in large doses paralyzes them; the endings of those fibers which are concerned with inhibition are not affected by ergotoxin. Here again we have an example of a drug acting on whole groups of nerve-endings which have similar functions; this results in constriction of the blood-vessels, with rise of blood-pressure, and in contraction of those smooth muscles which contract in response to stimulation of the sympathetic. It will be seen that ergotoxin resembles the action of epinephrin so far as the latter acts on the motor nerve endings, or myoneural junctions of the sympathetic, while it differs from epinephrin in that the latter also stimulates the myoneural junctions of the sympathetic which are concerned in inhibition, while ergotoxin does not.

As stated previously, in the discussion on epinephrin, the pregnant human uterus responds to sympathetic stimulation by contraction. It also responds to ergotoxin by contraction, and this serves to explain why ergot sometimes causes abortion, and also why accidents occur so frequently when ergot is used to empty the pregnant uterus, since overstimulation of the sympathetic results in tonic contraction instead of the peristaltic waves which are present in normal childbirth.

This tonic contraction, being desired after delivery of the placenta, also indicates the use of ergot at that stage of labor.

The uterus is more susceptible to the action of ergotoxin and epinephrin at the time of labor than during the non-pregnant state; hence ergotoxin, like epinephrin, then causes active uterine contraction with doses which have little effect on the general blood-pressure. Tonic contraction is the normal physiologic condition of the uterus after delivery of the placenta, and it is only natural that stimulation of the sympathetic has a more pronounced action at this stage than at a time when tonic contraction would be an abnormal condition, for it is a fairly general rule that drugs influence

structures more actively in the direction of their normal functions than in opposition to them.

Ergotoxin also acts on other smooth muscle which is innervated by the sympathetic, but these actions do not require discussion here.

Ergotinin, being inactive, does not require further discussion except to state that it may be converted into ergotoxin by hydration.

Tyramin, or hydroxy-phenyl-ethyl-amin, resembles epinephrin in its chemical constitution and its pharmacologic action. It is formed from tyrosin during putrefaction, from which circumstance it received the name "tyramin." It causes active contraction of the pregnant uterus, and probably constitutes the chief constituent of aqueous preparations of ergot, ergotoxin being insoluble in water.

Histamin may be derived from histidin; it is said to be present in ergot in amounts too small to influence the uterine action of the latter to any marked extent. It is so extraordinarily active on the uterus, however, that it is difficult to believe that it is without importance, though it may escape isolation in amounts that can be utilized profitably. It can be prepared synthetically, and may be obtained commercially, should further investigation indicate it has special value. It is said to cause a perceptible contraction of the uterus when that organ is perfused with a solution containing one part of the histamin in 200,000,000 parts of Ringer's solution.

It causes constriction of some vessels, but dilatation of others, the effect of its intravenous injection being a fall of blood-pressure.

In addition to the four constituents which have been discussed, ergot also contains saponin, which may be of some importance when preparations of ergot are injected intravenously, but which is of little or none when these are used orally. In addition, there are present minute amounts of various substances which have not been isolated in pure form.

It seems probable that all of the pharmaceutical preparations of ergot, both aqueous and alcoholic, which have decided therapeutic activity, contain either

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tyramin or ergotoxin, or both, and while the older nomenclature is confusing and should not be employed in prescribing, the following tabulation will show the relationship between some of these preparations and the active principles known to exist in ergot, as given by Barger and Dale:

Ecbolin and ergotin (Wenzell) mixtures of alkaloids, containing cholin (Meulenhoff).

Sphacelinic acid (Kobert): inactive resin with adherent alkaloid.

Cornutin (Kobert): an alkaloidal resin, probably containing some ergotoxin, and also some other active substance which may be a decomposition product of ergotoxin.

Cornutin (Keller): impure mixture of ergotin with ergotoxin.

Chrysotoxin (Jacobi): inactive yellow coloring-matter with a small proportion of adherent alkaloid.

Secalintoxin (Jacobi): mixture of ergotoxin and ergotin.

Sphaeclo toxin (Jacobi): impure ergotoxin.

Hydroergotin (Kraft): recent synonym for ergotoxin.

The foregoing tabulation may serve to suggest the un wisdom of prescribing every new preparation which appears with the claim that it represents the parent drug in a new and improved form. Among the numerous proprietary preparations which have been brought forward in recent years as substitutes for ergot is clavin, which was widely advertised for a time, and which has been shown to be a mixture of leucin and aspartic acid, and to be devoid of pharmacologic or therapeutic action.

Unfortunately there is no agreement as to the exact pharmacologic action desired when ergot is used therapeutically in many conditions other than childbirth, hence it is impossible to determine which of the several active principles should be used in its place in those cases.

Ergot exerts a marked effect on the central nervous system, the convulsions being due to this action, but this has not been studied sufficiently to make its consideration profitable. The depression which toxic doses induce in the cock is due apparently to the action on the cerebrum; the ataxia to action on the cerebellum; the central emetic action and the clonic type of convulsions suggest that the medulla is the seat of these actions.

The vagus center in the medulla is also stimulated, and the emesis which sometimes results appears to be

due to central action, for vomiting movements promptly follow the intravenous injection of ergot in eviscerated dogs; but much larger doses can be administered by the mouth without causing gastric disturbance.

The most striking effect of the injection of ergot in the cock is the gangrene of the comb and wattles which it induces. Ergot gangrene in man commonly affects the extremities. Many explanations have been offered to account for the phenomenon; but it can be said with certainty only that ergot exerts some peculiar action resulting in active contraction of the vessels (probably due to the ergotoxin and the tyramin in part) and that this is attended with stasis and hyaline thrombosis, with the resulting gangrene. Certain animals are much more susceptible to the gangrene action than others, the chicken, the pig and man being among those which are readily affected.

When fluidextract of ergot is injected directly into the veins it causes a slight and temporary fall of blood-pressure, followed by a brief rise, and then return to normal. The fall in pressure is due apparently to saponin and does not occur after the oral administration of ergot, because saponins are not absorbed rapidly, if at all, from the gastro-intestinal tract.

Small doses of ergot cause rhythmic contractions of the pregnant uterus, while large doses cause tonic contractions. Unfortunately, it is impossible to stimulate the rhythmic contractions by ergot without risk of inducing the tonic also; hence the danger of using ergot before the uterus has been emptied.

Ergot varies quantitatively, as well as qualitatively, in its actions, deterioration being quite rapid according to the general belief, but we have no biologic test which will indicate the therapeutic activity quantitatively; hence it is impossible to say how rapid the deterioration really is. One investigator estimated that ergot was but one-eighth as active after one year as at the time of being collected, and the pharmacopeia directs that it shall not be kept for more than one year. The liquid preparations of ergot deteriorate

also, but their rate of deterioration appears to be far more variable than is that of the crude drug. Preparations made with diluted alcohol and kept without exposure to the air keep fairly well.

The want of a chemical test for the activity of ergot has led to the introduction of various biologic methods of standardization; the most generally useful of these is probably that which consists in determining the amount of ergot required to cause gangrene of the cock's comb. The action on the uterus of the virgin guinea-pig would appear to have the advantage of testing the therapeutic activity on the organ for which the ergot is used therapeutically, but this test yields no more satisfactory results than does that on the cock's comb.

One or more of the principles which induce gangrene appear to deteriorate more rapidly than those which act on the uterus, and the test is therefore more suitable for fresh specimens than for old ones.

Acute poisoning with ergot is rare, if one does not include the untoward action on the uterus, but occasionally overdoses give rise to gastro-intestinal disturbances, convulsions and later to gangrene. There is no specific antidotal treatment for ergot poisoning, and one can only combat the symptoms as they arise.

THERAPEUTIC USES

Few drugs have been used in a greater variety of conditions than ergot, often where opposite effects are required; for example, in shock to increase blood-pressure, and in hemorrhage, where an increase in blood-pressure is contra-indicated.

It was formerly used extensively to hasten the expulsion of the fetus in normal labor, but one can never be certain of securing the increased rhythmic contractions and avoiding the tonic which prove so dangerous. Ergot should be used in labor only after the uterus has been emptied, to prevent or control post-partum hemorrhages. If used before the fetus or the placenta is expelled, only the smallest therapeutic dose should be employed, and this should not be repeated even if no effect is perceptible. This *use, however*, is strongly contra-indicated.

Ergot is used for excessive menstrual flow, and because it is useful in this condition it has been assumed that it would be equally useful in uterine hemorrhage from other causes, including that due to tumors, but there is no reason to expect favorable results in such cases.

There seems to be no sufficient reason for the continued use of ergot in any chronic condition, as it is liable to cause poisoning.

While ergot is capable of increasing the blood-pressure to a certain extent, it is inferior to epinephrin in this respect, and it is not sufficiently dependable for use in shock.

The other purposes for which ergot has been recommended do not appear to merit discussion.

DOSAGE

Ergot is commonly administered in the form of the fluidextract, which may be given by the mouth or injected intramuscularly—not subcutaneously, because of the pain which the last-named method involves. The action after oral administration is usually delayed for about twenty minutes; hence the intramuscular injection is preferable when post-partum hemorrhage is to be feared.

Not exceeding 2 c.c. (30 minims) of an active fluidextract of ergot should be administered before the expulsion of the fetus, but, as previously stated, even this is not recommended. This dose given after delivery of the placenta may be repeated if necessary after fifteen minutes. The dose required will depend largely on the activity of the specimen at hand, but it is better to have a reliable specimen always at hand for emergencies.

MATERIA MEDICA

Ergota.—Ergot, U. S. P.

In Continental pharmacopeias this drug is generally known as “secale cornutum.” It is officially described as the dried sclerotium of *Claviceps purpurea*, replacing the grain of rye. The drug as it occurs in commerce is derived chiefly from Spain and Russia, though other countries, notably Germany, Austria and Sweden occasionally furnish supplies of good ergot. Spanish

ergot is larger than the Russian variety, but is said to contain less ergotinin, which may be converted into the active ergotoxin.

Ergot deteriorates rapidly when kept in open vessels and in a damp atmosphere. This is particularly true of the powdered drug. The Brussels Conference Protocol and foreign pharmacopeias generally direct that ergot should not be more than one year old, and should be preserved entire. The powder when called for on prescriptions should be prepared at the time that it is wanted.

This drug is still frequently administered in the form of powder in doses of 1 to 2 gm. (15 to 30 grains) in the form either of capsules or cachets. It is more frequently administered in the form of:

Fluidextractum Ergotae.—Fluidextract of Ergot, U. S. P.

This preparation is a hydro-alcoholic, slightly acid liquid, having a reddish-brown color and a characteristic rather unpleasant odor. It is readily miscible with water, but precipitates slightly when mixed with an equal volume of strong alcohol. Considerable difficulty has been experienced in securing reliable and reasonably permanent fluidextracts or other preparations of ergot. Recent observations appear to indicate that samples of the fluidextract preserved in small vials or hermetically sealed tubes keep better than similar preparations exposed to the air, and the product at the present time is frequently dispensed in sealed vials or tubes containing from one to four doses.

Efforts to prepare purified extracts of ergot for hypodermic use or to isolate the active principles in water-soluble form have met with some success, and several preparations of this type now available are described in New and Nonofficial Remedies.

HYDRASTIS

This drug, its chief alkaloid, hydrastin, and hydrastinin, which is derived from hydrastin artificially, are often classified with the morphin group, but they act on the central nervous system much like strychnin. On the other hand, they are often used therapeutically

for their effects on the uterus: hence it is convenient to consider them here.

Hydrastis contains berberin and another unimportant alkaloid, canadine, in addition to hydrastin. The berberin probably has no especial value, but it is sometimes used for the effects of its bitter taste.

Hydrastin stimulates the central nervous system, overdoses causing hyperexcitability of the cord. Very large doses may cause strychnin-like convulsions. Moderate doses cause a rise of blood-pressure, probably through constriction of the arterioles; the mechanism of this is in some doubt, and its therapeutic importance has been greatly exaggerated. Toxic doses cause depression of the respiratory center and a fall of blood-pressure, with cardiac depression.

Hydrastis and hydrastin induce uterine contractions which may be peristaltic in character or they become tetanic: hence they are used to prevent excessive menstrual flow or uterine bleeding from other causes except post-partum hemorrhages, in which they are said to be much less effective than ergot. They are sometimes used in subinvolution of the uterus. It is possible that their tendency to cause a rise of blood-pressure may interfere with their therapeutic usefulness in arresting uterine hemorrhage.

They are commonly credited with some special tonic action on mucous membranes, and have been widely used, largely in the form of proprietary preparations, as applications to the nose, throat, urethra and vagina in chronic catarrhal conditions.

Hydrastinin acts locally and centrally to induce vasoconstriction, and at the same time it is said not to depress the heart; hence the general blood-pressure rises when it is injected. It is said to be better than hydrastin for checking uterine hemorrhage from various causes. It is sometimes used in solution for local application to various mucous surfaces to check hemorrhage. Its action on the uterus is much like that of hydrastin.

There is no very clear indication for the therapeutic employment of hydrastis and its alkaloids. Hydrastinin would seem to have the advantage over hydras-

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tis and hydrastin in nearly every case except those in which hydrastis is used for its bitter taste.

Hydrastis and its alkaloids afford an illustration of the way in which drugs of little therapeutic value attain wide popularity in the treatment of a variety of conditions. These agents have a great diversity of actions on the central nervous system, on the heart and vascular system and on mucous membranes. The proprietary preparations containing them have been lauded in many clinical conditions regardless of the fact that we have better drugs for nearly all of these conditions.

DOSAGE

The average dose of the fluidextract of hydrastis is 2 c.c. (30 minims); smaller doses may be used for the bitter effect; the dose of hydrastin or hydrastin hydrochlorid is 0.01 gm. ($\frac{1}{6}$ grain); that of hydrastinin is 0.03 gm. ($\frac{1}{2}$ grain).

MATERIA MEDICA

Hydrastis.—Hydrastis, U. S. P.

The dried rhizome and roots of *Hydrastis canadensis*, yielding by the process given in the U. S. P. not less than 2.5 per cent. of hydrastin. Hydrastis also contains about 3 per cent. of berberin and a minute quantity of canadine. The drug is used principally in the form of:

Fluidextractum Hydrastis. — Fluidextract of Hydrastis, U. S. P.

A solution of the soluble constituents of hydrastis in a mixture of glycerin, alcohol and water. One hundred c.c. should contain 2 gm. of hydrastin in addition to the other alkaloids of hydrastis.

Of the alkaloids occurring in hydrastis, only one is at all widely used. This is official as:

Hydrastina.—Hydrastin, U. S. P.

Because this alkaloid is almost insoluble in water, it is preferably used in the form of hydrastin hydrochlorid. It is hygroscopic and must therefore be kept in well-closed glass bottles.

Hydrastininae Hydrochloridum. — Hydrastinin Hydrochlorid, U. S. P.

An artificial alkaloid derived from hydrastin or made synthetically. It occurs as white or faintly yellowish crystals having an intensely bitter taste. It is very soluble (1:1) in water and freely soluble (1:3) in alcohol.

EMMENAGOGUES

The drugs intended to stimulate the menstrual flow were formerly treated at some length in text-books of therapeutics under the heading given above, but all of the emmenagogues have other actions on which their therapeutic use depends and they do not form a well-defined pharmacologic or therapeutic group.

Menstruation is attended with uterine congestion and is disturbed or prevented by numerous causes which interfere with the uterine circulation or with the general health. Hence emmenagogues may be classified as (1) measures intended to improve the general health; (2) measures or agents which promote uterine congestion.

Iron, strychnin and cod liver oil are frequently classified as emmenagogues which act by improving the general health, but it is obvious that this class must be nearly coextensive with the *materia medica*.

Among the measures intended to promote the uterine circulation are hot baths and irritants of the colon and of the genito-urinary tract.

Hot baths do not require detailed discussion in this place; the mechanism by which irritants of the colon, such as aloes and other evacuants of the anthracene group, cause uterine congestion will be discussed later; various volatile oils and other irritants which are excreted by the kidneys serve as irritants to the genito-urinary tract and induce uterine congestion, but their use is now limited almost entirely to users of patent medicine and mixtures intended to induce abortion.

These mixtures are usually fraudulent and the doses recommended seldom contain active constituents in dangerous amounts. Indirectly, the sale and use of such nostrums has resulted in many fatalities due to

the ingestion of dangerously large doses of volatile oils or of drugs containing them.

It is obvious from the foregoing discussion that the emmenagogues do not call for detailed discussion under this heading.

Valerian and viburnum may be discussed in this place.

Valerian is now believed to be useful in attacks of nervousness and hysteria by a psychic stimulation resulting from its disagreeable odor.

Viburnum prunifolium was formerly credited with the power to avert threatened abortion and to exert a favorable influence on menorrhagia. Reports sustaining these views have appeared in the literature, but the experience of most physicians fails to justify a belief in the qualities claimed for this drug. Viburnum contains small amounts of a volatile oil with a disagreeable odor and may act like valerian reflexly through the sense of smell.¹³

It is probable that viburnum prunifolium continues to maintain a certain degree of popularity because of extravagant claims made in advertisements in reputable medical journals by the manufacturers of various proprietary preparations such as Hayden's Viburnum Compound and Dioiviburnia. The advertising creates a certain demand for these preparations and the continued demand for them serves as a stimulus to pharmaceutical manufacturers to market more or less similar compounds for those who do not care to use the proprietary preparations, a sort of vicious circle of exploitation and demand being thus established.

13. The literature of these two drugs affords an example of the unsatisfactory conditions that obtain with reference to many articles in the materia medica as the result of the blind following of those who blindly copy others equally blind. Many text-books state or imply that the actions of valerian and viburnum are practically alike, but they also state that they are used therapeutically for unlike conditions. Thus valerian is commonly used for the relief of hysteria, while viburnum is often employed as a uterine sedative in painful and excessive menstruation and kindred conditions, but no explanation is offered for this difference in their application. One is almost forced to the conclusion that very little discrimination has been shown in the use of these drugs, and while accumulated clinical experience would *seem* to show that valerian has at least a limited field of usefulness, there is no apparent reason to retain viburnum in the materia medica in the absence of evidence that it has therapeutic value, and it would seem wiser to substitute valerianic acid for either of them in a given case. As a matter of fact, the whole subject requires investigation.

It seems probable that the ammoniated tincture of valerian will serve any purpose that the more expensive proprietaries may.

DOSAGE

Valerian is commonly administered in the form of the ammoniated tincture, in doses of 2 c.c. (30 minims), and viburnum is used in the form of the fluid-extract in like amounts.

Valeriana.—Valerian, U. S. P.

The dried rhizome and roots of *Valeriana officinalis*.

Tincture Valeriana Ammoniata. — Ammoniated Tincture of Valerian, U. S. P.

One hundred c.c. represent the soluble constituents of 20 gm. of valerian in aromatic spirit of ammonia.

CHAPTER VI.—DRUGS WHICH ACT MAINLY ON THE HEART

THE DIGITALIS GROUP

The digitalis group is one of the best defined in the materia medica because the cardiac actions of all its members are quite similar qualitatively, though they show wide quantitative differences and nearly all of the drugs of the group are used for their cardiac actions almost exclusively.

The characteristic action of these drugs on the heart is called the digitalis action, and all drugs exerting this action are called digitalis bodies, regardless of the source from which they are derived.

A drug is said to possess the digitalis action if it causes the frog's heart to come to a standstill with the ventricle in systole and the auricles in diastole, following a characteristic behavior. This usually includes a period of slowing of the heart-rate; a period of increased rate, and a period during which there are typical irregularities in the rate and force of contraction. The beat of the auricles and that of the ventricle usually show complete dissociation shortly before they stop. This digitalis action on the heart is interesting, for it exhibits all of the direct actions for which the drug is used therapeutically, except that on the vagus center.

Fatal doses of digitalis cause the intact mammalian heart to stop in diastole because it is incapable of beating after the coronary circulation is interrupted, but when the mammalian heart is perfused with a solution of a digitalis body it also stops with the ventricles in systole. This systolic standstill is an expression of the increased tonicity of the heart which is the foundation of the therapeutic use of the drug in a large proportion of cases.

Our knowledge of the drugs of this group has been extended greatly within the past few years with the

result that their therapeutic uses and limitations have been determined far better than those of most drugs. Digitalis, however, cannot be used successfully without an understanding of its pharmacologic actions, and there are few drugs concerning which there have been a greater number of erroneous conceptions. With the advance in our knowledge of the drug it has become necessary to revise much of the teaching that was current but a decade ago; therefore the pharmacologic and therapeutic actions of the digitalis bodies will be discussed in somewhat greater detail than those of many other important drugs.¹⁴

The digitalis bodies have no important direct actions on the higher parts of the brain, though they have a slight tendency to induce somnolence when large doses have been administered.

They stimulate the vomiting center in the medulla, and nausea and vomiting are commonly observed when the therapeutic dose is exceeded slightly with any member of the group, and it is difficult or impossible to elicit the full therapeutic effect of some of them without causing nausea. These symptoms afford a guide to the limitations of therapeutic doses, and these and other signs will enable the physician to elicit the full therapeutic effects on the heart while avoiding the dangerous side actions in the majority of cases.

Digitalis bodies stimulate the vagus center and the vagus endings in the heart, but the latter effect is probably of minor importance. The vagus stimulation does not always suffice to cause pronounced slowing of the heart-rate, but there is a group of cases in which it occurs almost invariably. These will be discussed later. Excessive doses cause an increase in the rate, with various forms of irregularity.

The rate of the heart-beat is controlled normally by impulses which arise in a small mass of tissue,

14. It may be remarked in passing that advances in our knowledge of digitalis have gone hand in hand with equal advances in our knowledge of the cardiac conditions for which the drug is useful, and physicians who are not familiar with the recent progress in the diagnosis and treatment of cardiac disease will find a little volume entitled "Clinical Disorders of the Heart," by Thomas Lewis, extremely valuable. The subject is discussed in a simple and easy manner which one can understand without being a specialist in cardiac diseases.

known as the sino-auricular node, or the pace-maker of the heart, which is situated in the region about the mouths of the great veins which empty into the auricle.

The impulses or stimuli for contraction which arise in the pace-maker pass down to the auricles, causing them to contract, and the impulses are then transmitted through the minute bundle of muscle fibers known as the auriculoventricular bundle to the ventricles, causing them to contract.

Digitalis depresses the conductivity of the auriculoventricular bundle, delaying or preventing the passage of impulses through it and causing what is known as heart-block. With moderate doses impulses are delayed, and a few of them may be prevented from passing; the block is then said to be partial. In such cases the interval between the beat of the auricles and that of the ventricles is increasingly prolonged with successive beats until one of the ventricular beats drops out, the auricles then beating three or four times to two or three beats of the ventricles. In such cases the ventricles may appear to be beating with almost perfect regularity, but careful observation will show a slight irregularity at least, and a difference between the number of the auricular and the ventricular beats.

With larger doses of digitalis there may be a complete block, so that impulses do not pass from the auricles to the ventricles, and the latter then take up an independent rhythm, usually much slower than that of the auricles.

Partial or complete heart-block may result from disease, or a small dose of digitalis may convert a partial into a complete block. This action of digitalis is exerted through the vagus, and it is interfered with by atropin.

Heart-block is beneficial in cases of auricular fibrillation, in which condition it relieves the ventricle of innumerable stimuli which cause it to beat irregularly and usually very rapidly, but it must be understood that digitalis has no perceptible influence on the fibrillating auricle, which continues to fibrillate *independently* of the improved circulation.

Auricular fibrillation is a condition which has only recently come to be recognized as of common occurrence in man, the condition being formerly diagnosed as myocarditis. The fibrillating auricle does not contract as a whole, but a fine tremor constantly involves the surface of the auricle, and instead of the rhythmic impulses which normally pass from the auricle to the ventricle, numerous impulses arise without any sort of order in the fibrillating auricle, and passing to the ventricle cause it to beat with extreme irregularity of rate and force, and usually very rapidly.

A heart which beats with abnormal rapidity does not contract adequately during systole, and the blood is dammed back into the veins, with the well-known evil consequences.

Digitalis causes the ventricle to beat more slowly, to dilate more completely in diastole, and to contract more forcibly and completely in systole, hence to empty itself more perfectly, discharging a larger amount of blood at each beat. It is easily understood that these changes result in a better circulation unless the slowing has been too great, and this improved circulation is the object of digitalis medication regardless of the symptoms of which the patient complains. There are few conditions in which digitalis is so dependable as in auricular fibrillation occurring in patients under 40 years of age.¹⁵

15. It may not be amiss to refer briefly to the means of diagnosing this condition, which is said to occur in 60 per cent. of the patients who enter the general hospitals with evident signs of cardiac insufficiency. It occurs rarely in those under 17 years of age, and not often before the fortieth year without a history of rheumatism or chorea. With advancing years it becomes more frequent in the absence of such a history. The most characteristic symptom is an absolute irregularity of the rate and force of the ventricular beat, that is, not even regularly recurring groups of beats can be made out. When a patient more than 15 years of age has a ventricular rate above 120 beats per minute at the apex and an absolutely irregular heart, one may strongly suspect auricular fibrillation. The occurrence of such symptoms in one who presents a history of rheumatism or chorea points even more strongly to that condition, and when to these are added other symptoms of cardiac insufficiency the diagnosis can be made almost with certainty. If the rate is slow but absolutely irregular the diagnosis may be aided by letting the patient take gentle exercise which causes the ventricle to beat more rapidly; the irregularity increases if the auricles are fibrillating, but decreases if it arises from other causes. Many beats can be heard at the apex which cannot be felt at the wrist, and the number of these is an index of the insufficiency of the heart. Auricular fibrillation usually persists from the time of its appearance until the death of the patient, but it is only temporary in about 10 per cent. of the cases.

If the heart is slowed to an excessive degree the volume expelled in a unit of time may be less than before the digitalis was given, but with moderate slowing which usually results, the improvement in the circulation is pronounced. It is impossible to state in exact terms what constitutes excessive slowing, but a reduction of 50 per cent. in the rate may be beneficial when the rate has been extremely rapid.

During cardiac dilatation, acute or chronic, the heart dilates excessively during diastole and contracts very imperfectly during systole, and much of its energy is then lost through the regurgitation of the blood through the incompetent valves. In such cases digitalis does not cause increased dilatation during diastole, but its capacity for increasing the tonicity of the heart becomes more prominent, and its effects are more pronounced in increasing the systole, whereby the amount of blood expelled at each beat is greatly increased. It is said by some to be much more effective in acute than in chronic dilatation, but others report good results in both conditions.

Since the heart rests only during diastole, the slowing of the rate, which is largely due to prolonged diastole, permits of a greater opportunity for rest. The blood is squeezed out of the tissues of the heart during systole, and when this is rendered more complete, a larger volume of fresh blood will flow through the capillaries and the heart will be nourished more efficiently. The opportunity thus afforded for the improved nutrition of the heart probably explains in part the increased force of contraction after digitalis, this being supplemented by the better general circulation in which that of the coronaries participates.

The complete recovery of the heart requires some time and the full *effect* of digitalis may be induced, slowly, even though its maximum *direct action* may be elicited promptly.

The mechanism of this increased nutrition should be borne in mind, for it will serve to explain why a rise of blood-pressure is seldom injurious to the heart even when the heart was previously overtaxed, for with the improvement in its nutrition the slight *additional* energy required to force the blood out

against the increased pressure will be more than compensated for by its increased capacity for contraction.

The effect of the digitalis bodies on blood-pressure has been the subject of a great deal of discussion. One difficulty which the investigation of this subject presents is that pharmacologists are unable to secure animals which suffer from cardiac diseases similar to those in which digitalis is used therapeutically, and we have seen that it tends to restore the heart-beat toward normal; hence the pharmacologic experiments have given conflicting results.

It is commonly stated that digitalis causes an increase in the blood-pressure, but it is true that it may produce the desired therapeutic effects while the blood-pressure rises or falls, dependent on whether it was previously too low or too high.

When the heart fails to supply enough blood to the central nervous system a greater or less degree of asphyxia with cyanosis results, and this causes constriction of the blood-vessels so that the increased blood-pressure may maintain a sufficient circulation in the central nervous system which must be supplied if life is to be maintained at all. Since the blood-supply elsewhere is insufficient, it is obvious that certain organs must suffer injury, one of these being the heart itself. When the heart begins to beat more efficiently the asphyxia is relieved, and the high blood-pressure may return to normal while the patient's condition improves.

When the vasomotor control of the pressure is impaired while the heart supplies an insufficient amount of blood, the blood-pressure is low, and such a condition must result in injury to some of the organs, especially the heart. When the heart-beat is improved in such cases by digitalis, the blood-pressure rises.

There is an extensive literature dealing with the constrictor action of the digitalis bodies on the vessels, especially concerning the capacity of certain members of the group to constrict the coronaries. This vascular action of the digitalis bodies is not very impor-

tant, but it has given rise to so much misunderstanding that it deserves a word of explanation.

All digitalis bodies act directly on the blood-vessels with which they are brought in contact *in sufficient concentration*, causing constriction; hence, when organs are perfused with blood or Ringer's solution containing any digitalis body in sufficient amount, the vessels are constricted, digitoxin being very active, while some other members of the group, notably strophanthin, are much less so relatively to their cardiac activity. It has been supposed that when these digitalis bodies are administered to patients they cause a similar vascular change, but this supposition is based on two erroneous conceptions. The first is that when digitalis is given in therapeutic doses, it enters the circulation in concentration comparable to that used in perfusion experiments, and the second is that the vasoconstrictor action persists for some time.

Digitalis has been shown to leave the blood-stream within a few minutes after its intravenous injection — and it acts on the vessels only while it is present in the circulating blood; in the next place it is never present in the blood of patients in the concentration in which it is used in perfusion experiments. From this one may say with a reasonable degree of assurance that the digitalis bodies exert no *direct* vascular action of any importance, and that when they exert any such action it is only through the general improvement in the circulation.

The diuresis which follows the use of the digitalis bodies is sometimes explained as being due to the constriction of the vessels of the liver and certain other areas, and dilatation of the vessels of the kidney. The renal vessels are normal in cardiac disease; if digitalis acted on them then it would affect them in the same way in health, but digitalis does not act as a diuretic in healthy men. Further, if it were capable of causing dilatation of the renal vessels some increase in the secretion of urine would be seen even in those cases in which digitalis failed to improve the condition of the heart; but, as a matter of fact,

diuresis does not occur when the drug fails to improve the heart-beat and the circulation.

There is no evidence whatever that digitalis has any direct action on the kidneys. The diuresis which it induces in patients suffering from dropsy due to the insufficient action of the heart is explained as follows:

When the heart fails to pump the blood from the veins into the arteries as rapidly as the veins supply it, certain organs begin to suffer, as previously stated, and water begins to pass from the circulating blood into the tissues in abnormal amounts; in other words, the patient becomes edematous. When digitalis causes an improvement in the action of the heart and in its capacity for removing the blood from the veins into the arteries, the water which previously tended to pass out into the tissues now begins to pass back into the veins, causing hydremia, and hydremia always causes diuresis if the kidneys are capable of secreting urine abundantly.

If the kidneys have suffered irreparably from the deficient circulation they may be incapable of secreting an additional amount of urine even though digitalis may cause some improvement in the heart-beat.¹⁶

The tardy appearance of the therapeutic effects of digitalis has long constituted one of the serious objections to its use. It has been taught that the delay is due to the slow action of digitalis after it comes in contact with the heart, but this is an erroneous view. Any delay in inducing the therapeutic actions of any of the members of the group in suitable cases must be attributed to the failure to secure the prompt absorption of an effective dose. The intravenous injection of a very large dose of any member of the group causes death by cardiac action within a few minutes, and sometimes within a few seconds, especially when digitoxin is used in excessive amounts,

16. Hydremia, however caused, as by the rapid absorption of water from the gastro-intestinal tract, causes a similar diuresis. The physician may convince himself of this by the simple experiment of drinking several glasses of hot water while avoiding active perspiration, and observing the amount of urine secreted. The experiment should be begun when the stomach is nearly empty.

though digitoxin was formerly supposed to be the slowest to act of any of the digitalis bodies in common use. The ultimate effects of digitalis action on the heart must be distinguished from the direct action itself.

Digitalis is absorbed within the course of a few hours fairly completely, a small part being probably destroyed in the gastric juice; strophanthus, or strophanthin, is absorbed very irregularly after the oral administration. Five times as much strophanthus as would be required by intravenous injection to cause death may be given by the mouth to a cat or dog without causing any perceptible symptoms as a rule, but occasionally rapid absorption and death will occur from such doses. A patient received six doses of strophanthus by the mouth in twenty-four hours without showing any effect that could be detected by the most careful observation with frequent pulse-tracings, but the seventh dose of the same amount as the previous ones was followed promptly by alarming symptoms of toxic action which continued for several days before improvement began.

These experiences both in the laboratory and in the hospital show that strophanthus and strophanthin are wholly unsuited for oral administration. Digitalis and its galenical preparations and digitoxin are the most absorbable of the digitalis bodies known.

CUMULATION, SO CALLED

When any digitalis body is given in repeated doses, toxic symptoms may appear rather suddenly, and these have been commonly attributed to cumulative action, so called, which has been looked on as a more or less mysterious property of the drugs which exhibit it. This so-called cumulation is nothing but the accumulated effects of several doses. The following will illustrate the action: A cat received 75 per cent. of the fatal dose of digitalis intravenously at one dose; a week later it received 50 per cent. of a normally fatal dose (or two-thirds as much as it had received a week previously), and succumbed promptly, the reason being that at least 50 per cent. of a *fatal* dose remained in the heart, or that the action

of that much remained in effect, and when 50 per cent. of the usually fatal dose was given its effects were added to those already present and the heart was brought to a standstill. A similar summation of effect results when several therapeutic doses are administered to man, and a given symptom appears when the added effects suffice to produce the symptom.

Laboratory experiments show that the effects of a single very large dose of digitalis or digitoxin may persist in part for two weeks or more, and clinical tests have shown that the effects of full therapeutic doses of digitalis may not completely disappear for ten days or more. The effects of strophanthin disappear much more rapidly, usually within from thirty-six to forty-eight hours.

Little is known concerning the fate of the digitalis bodies in the human body, but the persistence of the action on the heart and central nervous system suggests that some of them at least are destroyed or eliminated slowly. It is important to note, however, that they leave the blood-stream of all animals hitherto examined within a few minutes after intravenous injection, and they also appear to act on the blood-vessels only while they are present in the blood-stream.

STANDARDIZATION

We have no satisfactory means of standardizing the digitalis bodies; there is no chemical test for determining the amounts of the various pure principles present, and none of the biologic tests is free from objection.

The forthcoming Pharmacopeia will probably direct the standardization of digitalis bodies by means of the frog test, which consists in determining the amount required to cause the frog's heart to stop with the ventricle in systole in one hour. This test has the disadvantage of not affording a comparison of the therapeutic activities of such different members of the group as strophanthus and digitalis; for example, the amount of digitalis required to kill a frog of given weight by this method will have far greater thera-

peutic activity than the strophanthus required to kill a frog of the same size.

Guinea-pigs are preferred by some for standardizing these drugs, and the determination of the fatal dose by intravenous injection in cats has been suggested as affording a fairly satisfactory means of comparing the therapeutic activity of all digitalis bodies.

STABILITY

It has been generally taught that digitalis leaves and all of the galenical preparations of digitalis deteriorate rapidly despite any amount of care in preserving them. This appears to be one of the numerous errors in vogue regarding this drug, for digitalis leaves certainly retain their activity for many years with little loss, and the tincture also keeps extremely well if made with 70 per cent. alcohol. The infusion sometimes deteriorates rapidly, despite the addition of a small amount of alcohol, and it should not be kept for more than a week in warm weather.

Recent experiments have shown that an infusion of digitalis made without alcohol, filtered and bottled while hot, can be kept unopened in a warm room for several weeks with little loss of activity. The belief in the instability of digitalis and its official preparations has been fostered by those who exploit proprietary preparations of the drug with claims of greater activity and uniformity of action.

The loss of activity in digitalis preparations, such as the tincture, appears to proceed slowly for a certain length of time, and then to cease; it is probably due to the instability of some principle which is present only in small amount. This is not a serious objection, since one can use a little more of a tincture which has become weaker; and it is quite possible that the unstable body is responsible for a greater proportion of the side actions which all digitalis bodies exert, than of the therapeutic effects. Unfortunately, no one appears to have investigated the subject.

Among the curious misconceptions in vogue concerning digitalis is the belief that the tincture and the infusion have different therapeutic properties. The *tincture* represents the leaf fully, and so does the

infusion when it is made properly—which, however, is not always the case.

As a matter of fact, the use of the infusion of digitalis should be abandoned, since the tincture serves every purpose that the infusion does, and has the advantage of being more nearly uniform in activity, more stable, less expensive and requiring a smaller bulk for each dose.

THERAPEUTIC USES

There are few drugs which have more sharply defined uses than the digitalis bodies. They are indicated in all cases in which the tonicity of the heart is impaired, and while loss of tonicity is either the cause or the result of a large proportion of the symptoms observed in cardiac disease of long standing, there are stages of cardiac disease in which digitalis does harm. It probably finds its greatest field of usefulness in those cases of cardiac insufficiency which are induced by auricular fibrillation, and in acute dilatation, though it may cause improvement in chronic dilatation also.

It is not necessary to discuss the various symptoms which result directly and indirectly from impairment of the circulation, for serious impairment of the heart is usually attended with symptoms which direct attention to the heart at the time that digitalis is needed, and whatever the symptom which the patient complains of, whether it be difficulty in breathing, swelling of the legs or an unpleasant feeling in the region of the heart, the use of digitalis is based ultimately on its capacity for improving the heart's tonicity directly and indirectly through its causing heart-block and slowing with improved nutrition and added rest with recuperation of the heart.

Digitalis is sometimes used in the treatment of tachycardias which are not attended with auricular fibrillation, but it is seldom of benefit in paroxysmal tachycardia, especially in those cases in which the impulses arise in the ventricle, and when used in that condition its action must be watched carefully, and its administration discontinued when full therapeutic doses fail to cause improvement.

Heart-block has been mentioned as one of the effects of digitalis, and it might be supposed that this condition, when present, constitutes a contra-indication to the use of digitalis; but it is neither an indication nor a contra-indication for the drug. If a want of tonicity attends heart-block, digitalis may be used, even though it may convert a partial into a complete block.

Acute dilatation with its threat of impending death sometimes affords an opportunity for results that are positively brilliant, for occasionally such a patient will show marked improvement within a few minutes after the intramuscular or intravenous injection of strophanthin, and he may be restored to comparative comfort within a few hours.

Auricular flutter is a condition attended with an extremely rapid beat of the auricles and usually of the ventricles; digitalis converts this condition into one of auricular fibrillation, and at the same time heart-block is induced with the result that the ventricle is made to beat more slowly, in the manner already described. In some cases the ventricle is made to beat regularly and more slowly without heart-block apparently.

Digitalis bodies are contra-indicated in sinus arrhythmias, which are characterized by an irregularity of the whole heart, due to some abnormal condition in the sinus region.

It will be observed that nothing has been said in regard to the various valvular lesions as indications or contra-indications for the use of digitalis. This is because a valvular lesion alone is neither an indication nor a contra-indication for the drug. Various valvular lesions are found complicating other cardiac conditions, but so long as the heart maintains an adequate circulation it does not require digitalis whatever the lesion, and when it begins to fail owing to a want of tonicity it demands digitalis no matter what valvular lesion may exist, even aortic regurgitation being no bar to its use when loss of tonicity prevents it from maintaining an adequate circulation.

The most diverse views are held regarding the use of *digitalis* in pneumonia, diphtheria and other infec-

tious diseases. There can be no question that the tonicity of the heart is frequently impaired in such conditions, but it is obvious that digitalis has no direct action on the toxins which cause the injury to the heart. There is no reason to anticipate such excellent results from its use in these conditions as in auricular fibrillation, in which it removes the immediate cause of injury to the ventricle, and in acute dilatation, in which it inaugurates a cycle of improvement.

DOSAGE

Examination of various posologic tables inclines one to think that this question is in a confused state because of the great differences in the amounts of digitalis bodies advised by various authorities. The reason for these differences is not far to seek. Digitalis is given for a definite action, and it is given until that action is induced, or until the appearance of toxic symptoms indicates that the limits of safe dosage have been approached. Patients vary rather widely in the amounts required to produce a given effect, dependent somewhat on the way the drug is given.

The single dose of digitalis leaf is given as 0.065 gm. (1 grain), while that of the tincture is 1 c.c. (15 minims), which represents 0.1 gm. (1.5 grains) of the leaf. This inconsistency probably arises from a mistaken idea that the tincture does not represent the full activities of the leaf. The dose of the infusion is given as 8 c.c. (2 fluidrams), which corresponds closely with the dose of the tincture, but there is more ground for the belief that the infusion does not always represent the leaf fully.

It seems certain that we must sooner or later revise our methods of administering digitalis and its preparations.* An adult who has not had any previous medication will usually require a total of about 1 to 2 gm. (15 to 30 grains) of digitalis of good average quality, or the equivalent of the tincture—from 10 to 20 c.c. (from 2.5 to 5 fluidrams)—to produce the full therapeutic effects. Nevertheless we do not advocate such single doses as 10 c.c. (2.5 fluidrams) of the tincture.

* See Eggleston, *Arch. Int. Med.*, July, 1915.

No one should administer any dose of digitalis without observing the effects carefully, and stopping the administration or diminishing the dose when the therapeutic effects are induced, or when toxic symptoms indicate that the limits of therapeutic dosage are being approached. The following effects are to be especially noted as indicative of digitalis action, and as signs for diminishing the dose or discontinuing it altogether.

Slowing is fairly common, but it is not an invariable result, and disaster has resulted from persisting in the administration of digitalis because the rate failed to show the influence expected of the drug, for the rate may become more rapid with other toxic symptoms without preliminary slowing.

When the auricles are fibrillating, the rate at the apex and that of the wrist-pulse should be determined; the difference, known as the "pulse deficit," indicates the number of beats which are too feeble to be felt at the wrist, and in general denotes the relative efficiency of the heart. With improvement in the force of the heart-beat a larger proportion of the apex-beats can be felt at the wrist, so that the pulse deficit decreases, and the wrist-pulse may actually increase in rate, while the apex-beats diminish as the heart's condition improves with digitalis action. When all beats are felt at the wrist the maximum digitalis action is approached or reached. One should never make the mistake of counting the wrist-pulse alone in such cases.

Partial or complete heart-block is a fairly common symptom of digitalis action; coupled rhythm, or bigeminal pulse, during digitalis medication calls for its immediate discontinuance. The substitution of a regular rhythm for an irregular one also indicates therapeutic action.

While these signs of digitalis action are commonly attended with improvement in the patient's condition, some of them, the coupled beat, for example, may be observed even while the patient grows worse. The clinical symptoms alone cannot be depended on to *show the limits of dosage*.

The following clinical signs of improvement are valuable as showing that enough digitalis has been given, or that the dosage may be reduced: improvement in breathing (a patient who has been forced to sit up and who breathes with difficulty begins to breathe more easily and is able to sleep while lying down, while the cyanosis diminishes); marked increase in the amount of urine secreted while the intake of water is limited, and a simultaneous disappearance of edema; the diminution or disappearance of epigastric pain, and especially of tenderness and pain along the margin of the liver; the disappearance of nausea and vomiting. The latter symptom calls for a word of discussion because it is frequently misunderstood.

Venous congestion due to cardiac insufficiency is commonly attended with gastric disturbances, including indigestion, nausea and vomiting, and since one comes under treatment as his symptoms grow worse, it often happens that nausea and vomiting begin or are accentuated very soon after beginning digitalis medication, and they are then commonly attributed to the local action of the digitalis. It must be emphasized that *digitalis has no such local action on the stomach in doses which are used therapeutically*. If the administration is continued the nausea and vomiting will frequently stop with the appearance of other signs of improvement. One must therefore not take nausea and vomiting as a sign of the full digitalis action in the absence of the other signs mentioned above when it occurs early in the administration.

The following applies only to patients who have not had medication with any digitalis body during the previous two weeks:

One who suffers from cardiac insufficiency attended with auricular fibrillation may take 5 c.c. ($1\frac{1}{4}$ fluidrams) of a standard tincture of digitalis by the mouth at the first dose, and 1 c.c. (15 minims) every four hours thereafter until some signs of digitalis action are obtained. The patient must be watched carefully and the medication be discontinued at once when the therapeutic effects appear. This will serve

to induce the therapeutic effects in suitable cases within from twelve to twenty-four hours.

Strophanthin is suited only for deep intramuscular or intravenous injection, but it is especially useful where immediate action is essential, as in acute cardiac dilatation. The single and daily intravenous or intramuscular dose is from 0.5 to 1 mg. ($\frac{1}{120}$ to $\frac{1}{60}$ grain), preferably in 4,000 parts of normal salt solution, as concentrated solutions may cause considerable pain.

Crystalline ouabain (so-called crystalline strophanthin) acts like strophanthin, over which it has the advantage of greater purity and uniformity of action. The intramuscular or intravenous dose of crystalline ouabain is 0.5 mg. ($\frac{1}{120}$ grain); otherwise it is used like strophanthin. Both are now sold in ampules containing sterile solutions.

Neither strophanthin nor crystalline ouabain should be injected subcutaneously because such injections give rise to severe pain.

We believe that strophanthus and the tincture are unsuited for oral administration, for the reasons already given. The tincture may be given intramuscularly when strophanthin is not available, but the intramuscular dose of the tincture must be carefully regulated, for a single dose of 2 minims has caused death in a patient who had previously taken digitalis. It must be borne in mind that all digitalis bodies are strictly synergistic, so that half a dose of each of any two digitalis bodies constitutes a full dose.

The single or daily intramuscular dose of tincture of strophanthus is about 0.1 gm. ($1\frac{1}{2}$ minims), which should be well diluted with normal salt solution. This dose should not be repeated within twenty-four hours. Even this dose would be dangerous immediately after other digitalis medication.

The dose of true digitalin has never been determined, but it is too expensive for general therapeutic use; digitalein is not obtainable in pure form; consequently its activity is too variable to justify its therapeutic use. Digitoxin is somewhat less variable in activity, but the physical difficulties in the way of its use interfere with its intravenous and intramuscular

injection; it can be dissolved in alcohol or made into pills or tablets and used by the mouth. The dose is about 1 mg. ($\frac{1}{65}$ grain), and 0.5 mg. ($\frac{1}{125}$ grain) may be given thereafter at intervals of four hours, provided the patient is watched carefully for the signs of digitalis action, and the administration discontinued when these are observed. It is an extremely dangerous drug in the hands of those who are not skilled in the treatment of cardiac disease. The action of digitoxin is very persistent.

MATERIA MEDICA

Digitalis.—*Digitalis*, U. S. P. The dried leaves of *Digitalis purpurea*, collected from plants of the second year's growth at the commencement of flowering. European pharmacopeias generally direct that digitalis leaves be thoroughly dried and carefully preserved from moisture and light.

The powdered leaf represents the drug fully and is frequently administered in the form of pills, gelatin capsules or cachets.

The chemistry of digitalis is still imperfectly known. A number of so-called active principles have been isolated and several are now available in a commercial way. These include: true digitalin, digitalein and digitoxin. The products marketed as digitalin vary widely in composition and are sometimes differentiated by the designations "true," "German" and "French." The German digitalin is the preparation usually found on the market and is ordinarily dispensed when digitalin is prescribed. This preparation is a mixture of several glucosids, and its composition varies according to the method by which it is prepared. The more widely used and more reliable of the commercially available digitalis principles are described in N. N. R. Physicians who use these preparations should assure themselves of their nature and identity.

Digitalis is used principally in the form of:

Tinctura Digitalis.—Tincture of *Digitalis*, U. S. P. One hundred c.c. of the tincture represent 10 gm. of digitalis in diluted alcohol.

Infusum Digitalis.—Infusion of Digitalis, U. S. P. One hundred c.c. of the infusion represent 1.5 gm. of digitalis, with 10 per cent. of alcohol added as a preservative. Infusion of digitalis prepared recently from *powdered* leaves (not the bruised), but otherwise according to the pharmacopeial directions, represents the full activities of the leaf.

Strophanthus.—Strophanthus, U. S. P. The ripe seed of *Strophanthus Kombé*, deprived of its long awn. The seed of different species of strophanthus have long been used in Africa for the preparation of arrow poisons, but the drug and specimens of the prepared poison were first brought to Europe about 1860, and the seed used for the preparation of strophanthin about 1865.

The testimony concerning the therapeutic value of strophanthus has been conflicting, owing to the fact that it has been administered orally in nearly all cases, and its absorption is so variable. There is no question of the value of strophanthin when it is administered intravenously or intramuscularly in suitable cases.

Tinctura Strophanthi.—Tincture of Strophanthus, U. S. P. One hundred c.c. of this preparation represent 10 gm. of strophanthus in approximately 65 per cent. alcohol.

Strophanthinum.—Strophanthin, U. S. P. A glucosid or mixture of glucosids obtained from strophanthus. Strophanthin occurs as a white, or faintly yellowish, powder having an intensely bitter taste. Because of its toxicity great caution should be used in tasting it. It is very soluble in water and in diluted alcohol but less soluble in absolute alcohol.

Some of the unofficial varieties of strophanthus, notably *Strophanthus gratus*, contain glucosids that are more active than is the glucosid from the official variety of the drug. Gratus strophanthin, or, as it is sometimes called, crystallized strophanthin, is identical with ouabain, a glucosid obtained from *Acocanthera ouabaio*. While its pharmacologic action is considered to be qualitatively identical with that of the official strophanthin, it is more active and should therefore not be confused with the official drug. An

effort is being made to popularize the use of the name "ouabain" in literature in place of the various titles or synonyms that have been proposed, and physicians generally should lend their aid to this effort. The possible mistaking of "g-strophanthin," or of crystallized strophanthin for the official strophanthin might readily prove serious.

PROPRIETARY PREPARATIONS

The well-known disadvantages of all the digitalis bodies, especially their variability and their tendency to cause nausea and vomiting, have led to the introduction of numerous proprietary preparations, nearly all of which have been exploited with extravagant praise.

Digalen is claimed to be a solution of amorphous digitoxin, but no such substance as amorphous digitoxin is known to science, and several investigators have submitted evidence that digalen is either a solution of impure digitalein or of another substance with actions similar to it.*

It is sometimes claimed that the defatted tincture of digitalis is less actively emetic than the official tincture. The therapeutic dose of the official tincture of digitalis contains about 6 mg. ($\frac{1}{10}$ grain) or less of the fat—not enough to account for the emetic action; hence if a defatted tincture is less actively emetic than the official, it must be because it is a weaker preparation, containing less of the active principles of digitalis.

Digipuratum is an extract of digitalis from which inert matter has been removed and sugar of milk added to make it of the same degree of activity as the leaf. It was formerly claimed to be less actively emetic than the official leaf, but the claim is not substantiated by the results of pharmacologic experiments. It is many times more costly than the official leaf.

Digipoten is much like digipuratum.

Cumulation, so called, or persistence of action, is an inherent property of every digitalis body. Every

* See Report of the Council on Pharmacy and Chemistry, Jour. Am. Med. Assn., Sept. 5, 1914, p. 881.

digitalis body causes nausea and vomiting in overdoses, and no proprietary substitute has as yet been offered which is less nauseant in proportion to its therapeutic activity than digitalis.

In some cases persistence of action is a decided advantage in that, when once the action on the heart is induced, it obviates the necessity of further medication while the heart continues to improve.

The physician who uses digitalis leaf or tincture of good quality—and there is no difficulty in getting these of good quality—can have the satisfaction of knowing that with these he can accomplish all that can be accomplished with any digitalis preparation whether it be official or proprietary, except in those infrequent cases in which intramuscular or intravenous injections are required to avoid loss of time, and in such cases the official strophanthin or crystalline ouabain may be used.

CAFFEIN AND CAMPHOR

The pharmacologic actions of caffein and camphor have been discussed and attention has been called to the fact that we have no satisfactory explanation to offer for their use in cardiac disease.

Caffein may increase the tonicity of the heart, but it is practically impossible to regulate the dosage so that the action will be limited to that which is desired. It seems probable that any value which it may have in improving the circulation is due to its stimulation of the vagus, whereby the pulse-rate is slowed, and to its stimulation of the vasomotor centers, causing a rise of blood-pressure with the consequent improved nutrition of the heart.

It does not cause heart-block, which plays such an important rôle in the effects of digitalis in auricular fibrillation, but it may be of value in certain cases of acute cardiac dilatation, by reason of its action on the musculature.

The diuretic action of caffein results in the removal of a larger proportion of water than of salts from the circulation, and this facilitates the reabsorption of *fluid* from edematous tissues; hence caffein is useful

as an auxiliary to the digitalis bodies in dropsical conditions; but it should be used with caution, for caffein and the digitalis bodies have synergistic actions on the heart.

Camphor stimulates the medullary centers, and it is possible that its beneficial action in cardiac disease is due to the stimulation of the vagus and the vaso-motor centers.

While we are unable to state the exact dose of camphor which is suitable for use in these conditions, it is probable that much larger doses than those commonly advised will be needed, probably not less than 0.5 to 1.0 gm. (8 to 15 grains).

We would again call attention to the inadvisability of using caffein intravenously, even in urgent cases of cardiac disease, and to the advisability of injecting small doses *very slowly*, if it is so used.

CHAPTER VII.—CIRCULATORY DEPRESSANTS, DIURETICS AND DIAPHORETICS

CIRCULATORY DEPRESSANTS

It is well known that, though the blood-pressure undergoes frequent minor changes, it is under the control of a coordinated mechanism which tends to maintain a close approximation to a certain level from day to day during health. Even after the administration of drugs which affect the distribution of the blood, any considerable change in blood-pressure is usually only fleeting. When the vessels of the splanchnic region are constricted, those of the periphery usually undergo a compensating dilatation; if the constriction of the splanchnic vessels is sufficient to cause a rise of blood-pressure, the heart is commonly slowed, so that the pressure in the large arteries tends strongly to remain constant.

The blood-pressure may be lowered by diminishing the amount of blood in the circulation; by dilating the vessels, or by diminishing the activity of the heart by decreasing either its force or its rate.

Venesection, or bleeding, was formerly employed widely, but this has fortunately fallen largely into disuse.* Drastic cathartics were also used at one time somewhat more freely than at present; diaphoretics and diuretics remove liquid too slowly to be satisfactory in those emergencies in which vasodilators are commonly used. The blood tends strongly to maintain a uniform concentration, and when much fluid is removed by diuretics or diaphoretics this is largely replaced in the circulating blood by fluid drawn from the tissues.

* It is possible that the future development of the process of "vividiffusion" recently described by Abel and his associates may lead to a modified form of bleeding in therapeutics.

There is an even greater tendency on the part of the vasomotor mechanism to compensate for changes induced in the vessels of different areas, and the vasodilators often exert only an inconspicuous and brief influence on the general blood-pressure.

The rate of the heart-beat is influenced by many factors which tend to regulate it according to the demands of the circulation. Consequently, the heart often responds to the systemic actions of drugs in a manner directly opposite to that which would result from the action on the heart alone.

VASODILATORS: THE NITRITES

Therapeutic doses of many drugs cause dilatation of the vessels of certain areas, and many cause general vasodilatation when toxic doses are given.

Attention has been called to the dilator action of the antipyretics on the vessels of the skin whereby they promote sweating and the elimination of heat. They are not used to lower the general blood-pressure, however, even though this does result from their collapse action.

Alcohol also causes dilatation of the peripheral vessels even with small doses, and it was used formerly to lower blood-pressure. Toxic doses of hydrated chloral cause a marked vascular dilatation, and it is commonly stated or implied that therapeutic doses also lower the blood-pressure. Any such action, however, is commonly incidental to its narcotic effect and not due to its vasodilator action, which is unimportant except with toxic doses.

Guthrie is credited with having been the first to observe the effects of the nitrites in causing flushing of the face. Lauder Brunton is chiefly responsible for their introduction into therapeutics about 1867, after he had observed the effects of amyl nitrite on a patient who suffered from anginal attacks.

Tracings of the pulse taken by him after the administration of amyl nitrite during one of these attacks do not show any essential difference from tracings of the normal pulse, the amyl nitrite having overcome the vasoconstriction which accompanied the attacks.

The actions of the several nitrites, including amyl nitrite, glyceryl nitrate or nitroglycerin, which acts as a nitrite, and sodium nitrite, are qualitatively quite similar, though they differ somewhat in duration.

The nitrites have little direct action on the higher parts of the brain, except for the dilatation of the cerebral arteries. This is attended with a sense of fulness in the head and dizziness, with some disturbance of the special senses, and often with headache.

The effects on the medullary centers are direct and indirect, but it is not easy to determine which of these is the more important in some cases.

The vasomotor centers are certainly depressed after the administration of small doses of the nitrites, but this depression is probably not alone responsible for the vasodilatation which results, especially after large doses. The vessels of the face and neck—the so-called blush area—are affected first, and the vessels of the skin of the upper part of the body in general appear to dilate before the splanchnics, but these also participate in the effects of therapeutic doses.

There has been a good deal of discussion concerning the seat of the dilator action of the nitrites, and some authors attribute the effect almost entirely to the action on the musculature in the vessel walls, while others consider this wholly secondary and attribute the effect mainly to the depression of the vasomotor centers.

The question is of more than purely theoretic importance, because it is frequently stated that the nitrites have an especial action on the coronaries. It seems probable that they have no specific action on the coronaries, but that the benefit which they confer in conditions attended with high blood-pressure is due mainly to the relief of an overburdened heart by diminishing the resistance. Attention has already been called to the physiologic necessity for the coronaries to respond to increased cardiac action with dilatation when other arteries are constricted, from which it is evident that they do not behave toward all agents in the same way that other arteries do.

It is uncertain whether the nitrites have any important direct action on the other medullary centers,

though the functions controlled by these centers show active changes. It is sometimes stated that the vagus is depressed, leading to an increase in the heart-rate. The heart, however, responds normally to lowered blood-pressure by an increase in the rate of the beat.¹⁷ and it is not probable that vagus depression is due largely to the direct action of the nitrites. At any rate, it is important to remember that the heart is not injured by therapeutic doses of the nitrites, since these are used in precisely those conditions in which the heart suffers from overexertion.

After the administration of amyl nitrite the respiratory center behaves as it does during fall of blood-pressure from other causes, that is, it responds to the stimulation of carbon dioxid (or lack of oxygen), and increased respiration results. There is no reason to suppose that the nitrites stimulate the center directly.

The text-books state that enormous doses of the nitrites result in the formation of methemoglobin. This does not occur, however, with doses such as are used therapeutically; it is of no interest to the clinician, except in possible cases of poisoning.

Other smooth muscle beside that of the arterioles is depressed by the nitrites, and spasm of the bronchial muscles is said to be relieved by the fumes from the burning of potassium nitrate mixtures, which contain nitrites.

Hirschfelder has recently observed that the nitrites relieve intense intestinal peristalsis induced experimentally by the administration of lead and he maintains that since colic is associated with peristalsis and spasm the relief afforded by the nitrites in lead colic, tabetic crises and angina abdominis is due to their inhibition of intestinal movement rather than to any vasodilator effect.

The nitrites cause venous dilatation, and this probably contributes somewhat to the fall of blood-pressure, by providing reservoirs for the blood.

17. The tone of the vagus depends to a great extent on the blood-pressure in the medulla, and when this falls, the lowered vagus tone permits of acceleration through the action of the accelerator center. The delicacy of this regulating mechanism in the dog is such that it is extremely difficult at times to cause a notable fall in the blood-pressure by administering amyl nitrite to that animal, the heart becoming much faster with a slight fall. The rabbit lacks this delicate control and amyl nitrite causes a prompt fall of the blood-pressure.

The nitrites are oxidized in the body and appear in the urine chiefly as nitrates.

In addition to the effects of nitrites which have been discussed, other secondary effects will be observed at times,¹⁸ but these are inconstant, and are to be explained by the differences in the distribution of the blood which are seen at different times. If the renal vessels are dilated to a disproportionately greater extent than those of the general circulation, there may be an increased secretion of urine, but diuresis in such cases is not to be attributed to any direct action of the nitrites on the kidneys.

ACONITE

The actions of aconite are those of its principal alkaloid, aconitin, but tincture of aconite is used much more frequently than the alkaloid, because of the difficulty of obtaining aconitin of constant activity, and because of the inconvenience involved in the use of a drug of such extraordinary potency.

The actions of aconitin on the central nervous system are difficult of analysis, but these consist of stimulation and subsequent depression.

The heat-regulating center (if we may refer to the coordinating mechanism as a center) seems to be influenced by aconitin in the same way in which it is by the antipyretics, and aconite has a distinctly antipyretic action.

The vagus center is stimulated, and Cushny states that aconitin affords one of the best means of obtaining pure slowing of the heart. Fatal doses affect the heart partly through the vagus, and it is stated that larger doses of aconitin are survived if atropin be given than without it.

18. The question has been raised frequently whether the small amounts of nitrites present in flour bleached by the several processes in common use are injurious to health and whether flour bleached in this way is less digestible than unbleached. There is no evidence that minute amounts of nitrites are injurious, and it cannot be said that the flour so bleached is less digestible than the unbleached, but on the other hand, we are unable to say that small amounts of the nitrites continued over long periods are without deleterious influence on the health, and there still remains the larger subject on which there can be no discussion, that bleaching is often employed for fraudulent purposes.

Aconitin stimulates the respiratory center, but this shows a strong tendency to become depressed, and death from aconitin frequently results from paralysis of the respiratory center. So great is the tendency of aconitin to cause depression that it cannot be used therapeutically as a respiratory stimulant.

Vomiting often occurs late in the state of poisoning, this being due to stimulation of the vomiting center (unpublished experiments).

The direct action on the vasomotor centers does not appear to be constant, and there may be either reflex stimulation or depression, but there seems to be some evidence that vasodilatation is the more common effect of aconitin action.

The effect of aconitin on the heart is due to vagus and accelerator stimulation and to the direct action on the heart itself. There is apparently a brief period during which the heart beats more energetically because of accelerator stimulation, but this is unimportant, and with the slowing from vagus stimulation there is no corresponding increase in the strength of the contractions, so that less blood is expelled from the heart in a unit of time, and in consequence the blood-pressure falls. With severe poisoning from aconitin the heart becomes very irregular; in fact, various forms of irregularity are seen in the exposed heart of an animal poisoned with it, the heart finally stopping in diastole. It is more than possible that aconitin causes a fall of blood-pressure through its combined actions on the cardiac muscle, the vagus center and the vasomotor centers.

Aconitin causes tingling when applied to the tongue or to the skin in such a way that it penetrates to the sensory nerves, and when large doses have been taken this tingling is manifested in the same way as after local application. It is one of the most typical symptoms of aconite poisoning, and usually serves to call the patient's attention to something being amiss in such cases.

Aconite was formerly administered therapeutically to the point of commencing tingling in the fingers. The sensory stimulation is followed by anesthesia, but this

action is much less pronounced with aconitin than with cocain, or even than with atropin, to both of which aconitin is closely related chemically.

Aconitin is absorbed rapidly from the alimentary canal, and, to some extent, from the unbroken skin when applied in the form of an oleate or liniment.

Poisoning by aconite is not rare, but less frequent perhaps than formerly, when the drug was widely used for a great variety of complaints.

Absorption takes place so rapidly that there is usually little time for treatment after a fatal dose has been swallowed. Tingling and irritation of the mouth and throat are observed soon after the poison has been taken. This is due to the local action, and soon after the poison is absorbed the tingling is felt in the fingertips, and later over a large part of the body. Nausea, vomiting and diarrhea may occur. The respiration suffers severely as well as the circulation, and death probably results from a combination of the actions on the heart and the respiration.

Of course, any poison remaining unabsorbed should be removed from the stomach by washing; atropin is said to be antidotal, but it is probably of limited value in most cases, and artificial respiration would be preferable to the atropin action on the respiratory center. A single dose of 1 mg. ($\frac{1}{60}$ grain) of atropin may be given, and repeated once if it causes improvement in the respiration or if it fails to abolish the vagus influence on the heart.

The patient is kept as quiet as possible, and heat is applied to the body.

Tincture of aconite probably undergoes deterioration when kept long, and dogs sometimes withstand enormous doses even when these are injected intravenously. It is probable that the fatal dose of pure aconitin for a man is only a few milligrams.

THERAPEUTIC USES

The nitrites are used, as already indicated, for reducing blood-pressure. Amyl nitrite finds its especial field of usefulness in giving relief in attacks of *angina pectoris*, in which it is often supposed to

abolish spasm of the coronary arteries. It seems much more probable that amyl nitrite relieves this distressing and even terrifying condition by abolishing the excessive resistance against which the heart contracts.

It may be used to relieve any pain which is due to arterial spasm, to prevent or relieve epileptic convulsions, in bronchial asthma, and in lead colic.

Amyl nitrite is sometimes used to stop hemorrhage when this results from the rupture of a vessel in the lungs, brain or elsewhere through very high blood-pressure, but it is apt to do harm if the hemorrhage has progressed to a point where the general arterial pressure is already low. Owing to the brevity of its action it is unsuited to those conditions in which a prolonged effect is necessary.

Nitroglycerin is used much like amyl nitrite, but its action is not induced instantaneously as that of amyl nitrite is, and it is therefore employed where a slower and somewhat more lasting action is desired, as in the high blood-pressure of arteriosclerosis and of nephritis, as well as between the attacks of angina pectoris.

It is sometimes used with digitalis with a view to overcoming the reputed vasoconstrictor action of the latter. It has been brought out in the discussion of digitalis actions that this direct vasoconstrictor action is negligible, and that digitalis may actually cause a fall of blood-pressure when this was previously abnormally high.

It is probable that nitroglycerin is seldom of any benefit in influencing the action of digitalis.

Sodium nitrite is used for exactly the same purposes as nitroglycerin, and it probably has no advantages over the latter.

Erythrol tetranitrate (for description see New and Nonofficial Remedies) is used for the same purposes as nitroglycerin, over which it has the advantage of exerting a more prolonged action. It is very expensive, and is said to be even more prone than nitroglycerin to cause severe headache.

The vasodilator actions of alcohol have been referred to; spirit of nitrous ether has a feeble vaso-

dilator action, and is used to promote diuresis and diaphoresis.

In some cases the splanchnic vessels appear to be incapable of dilating in response to the action of the nitrites, and in such cases the slight fall in the blood-pressure, and probably some direct depression in the vagus center, result in such an increase in the heart-rate that the fall is converted into a temporary rise of pressure.

Aconite is used occasionally as an antipyretic and diaphoretic in fever patients of sthenic type, or early in other febrile conditions — not late during protracted fevers, such as typhoid. It may be used cautiously when it is desired to reduce the blood-pressure, if the heart is in good condition. There is little scientific basis for its continued internal use in therapeutics.

It is used externally in the form of liniments and ointments for the relief of neuralgias. Absorption may occur from the unbroken skin, and it should be used only with caution. It should not be applied to mucous membranes, from which it is absorbed promptly.

Veratrum viride is sometimes used for the reduction of the extremely high blood-pressure often seen in eclampsia. While good results have been reported in some cases, the action of the drug is not sufficiently understood to justify its use in general practice, and there is little reason to doubt that it sometimes precipitates a catastrophe in this dangerous condition. *Veratrum viride* is not recognized in "Useful Drugs," nor is it recommended here. It probably owes any popularity which it has to its former exploitation as a proprietary preparation under the name of "Norwood's Tincture."

DOSAGE

Amyl nitrite is commonly used in the form of glass capsules, or "pearls" containing from 0.2 to 0.3 c.c. (3 to 5 minims). These are carried about by the patient, and at the approach of an attack one of the "pearls" is broken in the handkerchief and the con-

tents inhaled. It is said that amyl nitrite causes less headache when inhaled through the mouth than when inhaled through the nose.

Amyl nitrite is sometimes sold in sealed glass containers holding about 25 gm. (1 fluidounce).¹⁹ These tubes should never be grasped in the bare hand. Before being opened they should be cooled, and wrapped in several folds of a towel loosely; the operator, when filing the neck, should point the tube away from his face.

Nitroglycerin being explosive, is commonly used in the form of the spirit or in tablets. The average dose of spirit of nitroglycerin is 0.05 c.c. (1 minim), which is to be repeated several times daily when it is desired to maintain the effect. It gradually loses its capacity for lowering the blood-pressure, owing to the development of habituation, and the intensity of the headache which it frequently causes is a great disadvantage in its use.

Spirit of nitrous ether, popularly used as a diuretic, has, to a limited extent, the vasodilator action of other nitrites, but is now seldom used. The average dose is 2 c.c. (30 minims).

The dose of sodium nitrite is about 0.05 gm. (1 grain) repeated several times daily. It is always administered in solution, but it is prone to undergo oxidation with the formation of the nitrate; hence only enough of the solution should be prepared to last a short time.

Aconite is almost invariably administered in the form of the tincture, of which the dose is 0.2 c.c. (3 minims) repeated every hour until the desired effect is produced, or until its uselessness for that case is demonstrated. Smaller doses may be given with correspondingly greater frequency.

19. The following experience may be of interest: The neck of one of these tubes was filed with the intention of opening it, when it exploded violently; a second tube was cooled in a freezing mixture of salt and ice, and the neck then filed; there was a severe explosion; several tubes were then opened after wrapping them in towels, but in every case explosions of extreme violence resulted. The makers are well-known chemists, but they have been unable to explain the extreme violence with which these tubes exploded.

MATERIA MEDICA

Amylis Nitris.—Amyl Nitrite, U. S. P.

A volatile and inflammable liquid consisting chiefly of isoamyl nitrite. It should be kept in hermetically sealed glass bulbs, or "pearls," or in dark amber-colored glass-stoppered vials in a cool and dark place. Amyl nitrite occurs as a clear yellowish liquid, of a peculiar ethereal, fruity odor, and a pungent aromatic taste. It is never given internally by mouth, but is administered by inhalation.

Spiritus Glycerylis Nitratis.—Spirit of Glyceryl Trinitrate, U. S. P.—Spirit of Nitroglycerin.—Spirit of Glonoin.

An alcoholic solution containing 1 per cent. by weight of glyceryl trinitrate. It should be carefully preserved and stored in a cool place remote from light or fire. Spirit of glyceryl trinitrate occurs as a clear, colorless liquid having the odor and taste of alcohol. It does not mix clear with water but is miscible in all proportions with alcohol. It is best administered alone in water.

Spiritus Ætheris Nitrosi.—Spirit of Nitrous Ether, U. S. P.—Sweet Spirit of Niter.

An alcoholic solution of ethyl nitrite containing not less than 4 per cent. of the pure ether. Spirit of nitrous ether occurs as a pale yellowish or faintly greenish-yellowish liquid having a fragrant, ethereal and pungent odor free from acidity, and a sharp burning taste. When freshly prepared, it is neutral to litmus paper and is miscible with alcohol or water. The preparation deteriorates rapidly.

Sodii Nitris.—Sodium Nitrite, U. S. P.

The official sodium nitrite is required to contain not less than 90 per cent. of NaNO_2 and is directed to be kept in well-stoppered bottles. It occurs as white or nearly white opaque fused masses or colorless crystals, odorless and having a mild saline taste. It is freely soluble (1:1.1) in water, but only slightly soluble in alcohol.

Aconitum.—Aconite, U. S. P.

The tuberous root of *Aconitum napellus* L., used preferably in the form of:

Tinctura Aconiti.—Tincture of Aconite, U. S. P.

One hundred c.c. represent 10 gm. of the drug in approximately 65 per cent. of alcohol.

This preparation is occasionally used as a local application either alone or in mixtures with from 4 to 9 parts of soap liniment.

COLCHICUM *

The actions of colchicum are due to its alkaloids,† colchicin and colchicein. These are of some toxicologic importance, but what is known of their actions does not serve as a rational basis for the therapeutic use of colchicum, which is employed empirically in the treatment of gout and rheumatism.

When colchicum (or colchicin) is taken by the mouth or injected subcutaneously, no effect is observed for from three to six hours, however large the dose. This peculiarity has been explained on the theory that colchicin itself is not toxic, but that it must undergo oxidation to form the poisonous oxydicolchicin. Another suggested explanation of the delay in the onset of symptoms is that the poison is absorbed slowly by the central nervous system, the delayed action of tetanus toxin being cited by way of analogy.

Colchicum and colchicin are actively irritant to subcutaneous tissues and to certain mucous membranes. They cause gastro-intestinal irritation with nausea, vomiting and diarrhea. The stools resemble ordinary watery evacuations at first, but later they may become bloody.

In addition to the irritant action on the intestine, colchicin is said to act like pilocarpin and physostigmin on smooth muscle, increasing intestinal peristalsis and the contraction of the bronchial, and other, musculature, but it does not affect the heart directly.

Nephritis is sometimes induced, but the effects on the kidney are inconstant, probably dependent on the

* This drug bears little relation to the others of this group, but it is considered here for convenience.

† Colchicin and colchicein are classified as alkaloids, though they also have acid properties.

degree to which elimination takes place by way of the intestine.

The circulation is not affected to an important degree early in the course of poisoning, but Dixon and Malden state that death results in colchicin poisoning through paralysis of the vasomotor centers. Others maintain that death results from paralysis of the respiratory center.

Falck collected statistics of fifty-five cases of poisoning by colchicum, and it is said to occur in Germany through the careless gathering of the herb.

The stomach and intestine should be emptied after a poisonous dose of colchicum has been swallowed if it is discovered in time, that is, before the symptoms develop. Wood states that tannin is the only possible antidote, but that it is not dependable. If the drug has been absorbed, the treatment must be symptomatic, since the early vomiting and diarrhea will serve to remove any that may have escaped absorption.

It is commonly stated that as little as 3 mg. ($\frac{1}{20}$ grain) has proved fatal to a patient suffering with gout and nephritis.

A case of poisoning has been reported in which a robust man took a nostrum containing colchicin in the hope of averting an anticipated attack of gout. It is said that a total of 34 mg. ($\frac{1}{2}$ grain) of colchicin was taken in a period of nineteen days. Paralysis then began in the hand, and within twelve days involved the entire trunk and the limbs. The symptoms were followed by rapid improvement.

THERAPEUTIC USES

Colchicum is used mainly to avert attacks of gout or to abate their severity. It relieves the pain and swelling in the joints, and seems to shorten the duration of the attacks. Von Noorden believes that it is useful in gouty seizures, but that it is useless in the intervals between attacks as well as in chronic and atypical gout.

It seems to have some analgesic action in rheumatism, but it is not used so commonly in that affection *as in gout*.

It does not appear to have any important or constant influence on the elimination of uric acid, but the testimony on this subject is somewhat conflicting.

DOSAGE

The pharmacopeia states that the average dose of colchicum seed is 0.2 gm. (3 grains), and that that of colchicin is 0.5 mg. ($\frac{1}{130}$ grain); but the seed is required to contain 0.55 per cent. of colchicin, and hence the dose stated for the seed contains more than 1 mg. ($\frac{1}{65}$ grain) of colchicin.

It would seem to be unwise to give more than 3 mg. ($\frac{1}{20}$ grain) of colchicin daily, whether one uses the seed, the tincture of the seed or the alkaloid itself, and the administration should be interrupted or the dosage diminished if diarrhea is induced.

The average dose of the tincture is 2 c.c. (30 minims), which contain 1 mg. ($\frac{1}{65}$ grain) of colchicin.

MATERIA MEDICA

Colchici Semen.—Colchicum Seed, U. S. P., is generally used in medicine in the form of:

Tinctura Colchici Seminis.—Tincture of Colchicum Seed, U. S. P. A hydroalcoholic preparation representing 10 w/v per cent. of colchicum seed and containing approximately 0.05 per cent. of colchicin.

DIURETICS

The secretion of urine may be influenced by drugs in many different ways; hence the diuretics do not constitute a well-defined group, and in fact, few of them are used as diuretics exclusively. Some of the diuretics have been discussed among other groups, and others will be discussed elsewhere.

Sollmann²⁰ classifies the diuretics as follows:

1. Those acting through changes in the general circulation.
2. Those acting purely by local irritant stimulation of the kidney cells.

20. Sollmann: Pharmacology, Philadelphia, W. B. Saunders Company, 1906, Ed. 2, p. 546.

3. Those acting by non-irritant stimulation of the kidney cells.

4. Those acting mainly by salt action.

Under normal conditions the rate at which the urine is secreted varies with the volume of blood which passes through the kidneys in a unit of time, but there is a minimum blood pressure (about 40 mm. of mercury), below which the kidneys do not function. On the other hand, intense constriction of the renal arteries causes a diminution of the secretion even though the general blood pressure may remain high.

The actions of the digitalis bodies have been discussed and it is necessary to call attention here only to the fact that they cause diuresis by improving the circulation. There is no evidence that they act on the kidneys directly, and in fact they do not cause diuresis in healthy man, since they do not improve the normal circulation.

VASODILATORS

While our knowledge of the actions of the vasomotor nerves in controlling the circulation is considerable, we do not know much about the changes which drugs cause in the renal circulation under different conditions, unless they induce diuresis, which may be accepted as evidence that the circulation has been improved. But improvement usually means only a closer approximation to normal conditions, since either vasodilatation or vasoconstriction may interfere with the secretion.

We may conclude then that the vasodilators will facilitate the secretion of urine when they abolish an excessive constriction of the renal arteries without causing too great a fall in the general blood pressure, but we are unable to state in what cases this beneficial effect will follow their use. The nitrites and other vasodilators have been employed in many cases in which they could hardly be of benefit, for example, they have been recommended frequently to overcome the vasoconstrictor action of the digitalis bodies, but, as we have already pointed out, the *direct* vasoconstrictor action of therapeutic doses of the digitalis bodies is wholly negligible, and when an improvement

in vascular tone follows their use it is due to the general improvement in the circulation, and does not call for vasodilators.

It is hardly probable that the vasodilators can often have any important action in promoting diuresis, but the indications for their use in any case may be deduced from the discussion of their actions.

The drugs of the caffein group influence the general circulation but their most pronounced diuretic action is exerted on the kidney directly.

IRRITANTS

The second class of drugs—those which act through their local irritant action on the renal cells—embraces the volatile oils, which have been mentioned under urinary disinfectants, and certain glucosidal bodies, such as scoparin, and some others which are not used therapeutically for their diuretic action.

The most important drug usually classed among the irritant diuretics is calomel. There is no question that large doses of calomel are capable of causing renal irritation, hence caution is urged when it is employed in nephritis, and some authorities state that it should not be used when there is the least suspicion of nephritis. That view would appear to be extreme, however.

An entirely different theory has been advanced recently to account for the diuretic action of calomel. It causes increased peristalsis in the small intestine resulting in a lessened absorption, and consequently in the emptying of a larger amount of fluid into the colon than normally. It is explained that calomel does not affect the large intestine markedly, and the excess of fluid in the colon undergoes rapid absorption. In the meantime the composition of the blood has been restored to the normal through the withdrawal of fluid from the tissues to compensate for that excreted into the small intestine, and this rapid absorption of fluid from the large intestine induces hydremia and consequent diuresis. It is urged that the copious diuresis which accompanies the absorption of small amounts of calomel prevents the latter from exerting its irritant action on the renal cells.

It is a matter of common experience that calomel diuresis is attended with greater improvement in the condition of dropsical patients, than is seen when it causes the removal of water by purgation.

There is no apparent advantage in securing the absorption of water from the colon only in order that it may be excreted by the kidneys, hence we must suppose that the advantage is due to a milder action whereby the sudden removal of a large amount of fluid from the circulation is avoided.

The combination of opium and calomel causes diuresis more certainly than does calomel alone, and this is explained on the basis that the delayed peristalsis permits of a greater absorption of calomel, or according to the view of calomel action just discussed, it permits of a greater absorption of water from the large intestine.

Several investigators have found that a given amount of water administered by the mouth causes a greater diuresis than an equal amount injected intravenously or subcutaneously. It has been suggested that some substance which is actively diuretic, is absorbed with the water from the intestine, and that it is the absence of this hypothetical substance in the circulation which accounts for the slighter diuresis when the water is injected intravenously. It is probable that the diuretic action of calomel may stand in relation to this observation.

CAFFEIN GROUP

The drugs of the caffein group are the only ones of importance which induce diuresis through their non-irritant stimulation of the renal cells.

We have called attention to their influence on the heart, and on the vasomotor system, and it remains to discuss their specific action on the renal cells.

It is generally held that they act on the tubules, stimulating them to increased secretion, but there is another theory of their action which is diametrically opposed to this view, according to which caffein inhibits the capacity of the tubules for reabsorbing water, with a consequent increase in the amount eliminated.

Whichever theory is correct, the essential fact for the clinician is that caffein and theobromin act on the kidneys and do not cause irritation, hence they may be used in the presence of chronic nephritis. While this statement applies to theobromin, it does not seem to be true of theobromin and sodium salicylate.

It is sometimes maintained that these agents cause a specific dilation of the renal vessels, but the vessels of every organ dilate when it begins to function more actively, and it is impossible to say whether the renal dilation is the cause or effect of renal activity.

OTHER MEANS OF CAUSING DIURESIS

The rate of secretion of urine varies with the viscosity of the blood, and anything which causes water to pass into the circulation tends to promote the secretion of urine. This may be accomplished by causing water to be absorbed from the body tissues or from the alimentary tract.

The absorption of tissue fluids into the circulation may be accelerated during health by the intravenous injection of a saline solution which has a higher concentration than the blood. The renal cells offer little resistance to the passage of sodium sulphate, and when a 2 per cent. solution is injected intravenously, tissue fluid passes into the circulation and active diuresis is induced. This is one of the most active diuretics at our command, and may be depended on to hasten the elimination of those poisons which are excreted by the kidneys. Obviously, this method is only suited for emergencies.

Venous stasis favors the passage of water from the blood into the tissues, and conversely, the relief of venous stasis is commonly followed by the return of the water from the tissues into the circulation, with the resulting hydrema and diuresis.

Even a comparatively small initial change of this sort may institute diuresis with the ultimate elimination of enormous quantities of water with progressive improvement in the circulation and relief of the stasis; hence any drug which causes improvement in the general circulation in dropsical conditions will act as a diuretic if the kidneys are capable of functioning.

Owing to the slight absorbability of sodium sulphate by the intestinal epithelium it does not usually pass from the intestinal tract into the circulation with sufficient rapidity to cause active diuresis, but the acetate and citrate of potassium are absorbed promptly and are commonly used as diuretics. They are also commonly used when it is desired to render the urine alkaline.

Potassium acetate is absorbed more readily than the citrate, and is therefore a more active diuretic; large doses of the citrate act as a laxative, and may then fail to produce diuresis, and may even diminish it temporarily, since the removal of water by the bowel will increase the viscosity of the blood.

THERAPEUTIC USES

The urine serves to remove toxic substances from the body, whether these be waste products formed during health, the results of disease, or poisons introduced in the form of drugs, though not all toxic substances are removed in this way. From this the chief uses of the diuretics in normal circulatory conditions are obvious. When the circulation is impaired and water accumulates in the tissues, it causes distress, and its removal becomes imperative. This may be accomplished in part by sweating and purgation, but diuresis affords the most satisfactory method of disposing of the accumulations when the kidneys are capable of functioning normally.

It is not feasible to consider all of the therapeutic indications for diuretics, and only a few of them will be discussed here.

We do not know enough about the toxic substances (toxins) which are formed during disease and the best method of securing their elimination to enable us to state just what measures should be employed, and therefore we do not know to what extent the use of active diuretics will prove beneficial in many cases. We know that certain vegetable poisons at least are excreted practically unchanged in the urine, while others are decomposed to a greater or less extent before they are eliminated, and still others are removed from the circulation by the liver, and exert

practically no effect on the kidneys, and their elimination is practically unaffected by diuresis.

Our knowledge of the fate of many of the vegetable poisons is fragmentary, and we are often unable to state whether they are eliminated by the kidneys, or by the liver, or are destroyed in the organism.

Even in those cases in which we know that a poison is eliminated by the kidneys, we are seldom able to state whether it is excreted through the glomeruli or through the activity of the tubular epithelium, hence we do not know which of the diuretic drugs is to be preferred in a given case. Fortunately, diuresis, however induced, appears to favor the elimination of many of those poisons which are excreted through the kidneys, and the necessity of choosing one diuretic rather than another does not appear to be pressing, and in cases of acute poisoning by a drug such as strychnin, which is excreted mainly by the kidney, and when the necessity of securing its rapid elimination is urgent, one's efforts should be directed toward inducing copious diuresis by the most effective means at hand.

When poisons which are capable of inducing nephritis have entered the circulation, it seems probable that we should secure the largest possible flow of blood through the kidney vessels, as well as the most copious diuresis; hence caffein and theobromin, which are said to cause a specific dilation of the renal vessels, probably deserve consideration in addition to other diuretic measures.

It is surprising how little attention has been paid to the possibilities of extreme diuresis and flushing of the kidneys to the maximum in cases of poisoning with mercuric salts, which have become all too common of late, but it is not to be understood that this subject has been wholly neglected, and diuresis does play an important rôle in the treatment in such cases. We do not believe that the possibilities of the treatment have been appreciated, however, just as the possibilities of the elimination of strychnin during intense diuresis have been overlooked, even though every text-book mentions diuretics as a part of the routine treatment in such cases.

The choice of diuretics in a given case is often empiric though there are certain conditions which demand a definite method of procedure.

When there is an accumulation of water in the tissue (dropsy) due to the faulty action of the heart and its failure to maintain an adequate circulation, the digitalis bodies are of the first importance, and their action may be supplemented advantageously by that of caffein. The different drugs of the digitalis group contain irritant principles and it is barely possible that some of these may induce diuresis after the manner of the second class mentioned above, that is, those acting purely by their irritant action on the renal cells, but the evidence against this has been cited. The irritant digitalis principles are probably excreted almost entirely through the liver, and when they are excreted through the kidneys this appears to take place so slowly that they are never in sufficient concentration to cause severe irritation. At any rate the digitalis bodies do not cause serious renal irritation and they are used in the presence of nephritis.

The action of the digitalis bodies may be supplemented by diuretics which cause dilation of the renal vessels (caffein), or by those which cause hydremia (calomel, potassium acetate).

Just as digitalis bodies are indicated when the cardiac action is impaired, so they are contra-indicated when the heart beat is normal, and in such cases dependence should be placed in drugs which diminish the viscosity of the blood, or those which act on the kidneys directly when diuresis is desired.

There is seldom any special indication for the use of the volatile oils as diuretics alone, but they are sometimes used in small doses which produce only a mild stimulation of the kidney cells.

The injection of physiologic salt solution commonly causes a marked diuresis, but the kidney may become resistant to the passage of sodium chlorid as the result of continued administration or under pathologic conditions, in which case the administration of salt leads to a diminution of urinary secretion. It then becomes

necessary to reduce the ingestion of salt to a minimum. Attention has been called recently to the slow intravenous injection of hypertonic solution of glucose when sodium chlorid is contra-indicated.

Venous engorgement involving the abdominal veins which results from cardiac insufficiency, interferes with the renal circulation by retarding the outflow, and, as is very well known, anything that interferes with the free outflow from the renal veins interferes with the secretion of urine. Hence anything which relieves the venous stasis promotes the secretion of urine.

Active cathartics which remove a large amount of water may suffice to relieve the interference with the renal circulation. In like manner dropsical accumulations may interfere mechanically with the venous return and thereby lessen the secretion of urine, and in an analogous manner the purgative sometimes affords relief by removing the water which presses on the veins.

Clinicians often experience great difficulty in removing accumulations of fluid in patients who suffer with renal insufficiency. The retention of urea in nephritis is so well known as to require no further comment.

Saline diuretics and drugs of the caffein group are said to be best for use during chronic nephritis.

DOSAGE

The dosage of the digitalis bodies has been discussed in the article dealing with cardiac drugs.

The dosage of caffein and theobromin for inducing diuresis is commonly limited by its actions on the heart and central nervous system, especially in the case of caffein by its tendency to produce wakefulness, and in the case of theobromin by its action on the heart.

The diuretic dose of caffein is usually given as 0.3 gm. (5 grains) but the drug is commonly given up to the limitations imposed by its side actions. It may be repeated about three times a day. Theobromin is given in about the same amounts, but owing to the

more rapid action it may be repeated about four times a day.²¹

Much larger doses of theobromin and sodium salicylate have been used, and Taylor has recently stated that 5 gm. (80 grains) is a normal daily dose, in patients suffering with myocardial disease. Smaller doses were found unsatisfactory.

The volatile oils are seldom administered alone for their diuretic action, but they are sometimes used in the form of infusions, or other preparations of drugs which contain them.

The dose of potassium acetate is about 2 gm. (30 grains). It is commonly used when it is desired to increase the urine and render it alkaline, and the dose may be repeated every two or three hours until the desired object is attained. It is converted into the carbonate, in which form it is excreted largely.

Calomel is given in doses of from 0.1 to 0.2 gm. (from 1½ to 3 grains) several times daily when it is desired to cause diuresis. Since such doses cause diarrhea in most cases, it is often advised that opium be administered with it in sufficient amounts to prevent active purgation. This interferes with the evacuation of large amounts of water, and does cause diuresis in the manner described, but it is probably better to use smaller doses of calomel, and avoid the necessity of using opium. In many cases the removal of even a small amount of water by purgation will suffice to inaugurate an increased secretion of urine, and with a mild action one avoids the depression which is such an objectionable feature of violent calomel purgation.

21. It seems probable that theobromin may be administered conveniently in the form of cocoa in sufficient amounts in many cases. It is often objected that this requires the administration of too much water, but every patient must have some fluid every day, and since cocoa should be made with milk only—not with water—there is no apparent reason why the cocoa should not be administered with the milk which forms an important part of the diet as a rule in such cases. The better class of powdered cocoas contain about 1 per cent. of theobromin, hence 10 gm. of powdered cocoa, sufficient for one cup, would contain 0.1 gm. (1½ grains) of theobromin. If desired, the theobromin administered in this way may be supplemented by theobromin or the theobromin and sodium acetate or salicylate. An advantage in the use of cocoa in this way is the reduction of the amount of sodium salicylate or acetate which it presents, and the lessened gastric disturbance.

Small doses of calomel often cause purging with little more discomfort than accompanies a normal movement. The severe depression which accompanies calomel purgation is probably due in a large measure to the determination of an excessive amount of blood to the splanchnic region as the result of active intestinal secretion. Moderate doses are not accompanied by this excessive activity of the intestinal glands and the resulting depression.

It seems probable that the combined use of digitalis, calomel and caffein or theobromin would be better than calomel with opium, except when the opium is needed for its other actions.

MATERIA MEDICA *

Potassii Acetas.—Potassium Acetate, U. S. P. It should contain not less than 98 per cent. of pure potassium acetate ($\text{KC}_2\text{H}_3\text{O}_2$). It occurs as a white powder or in crystalline masses, odorless and having a saline taste. Potassium acetate is deliquescent on exposure to air. It is very soluble (1:0.4) in water and freely soluble (1:2) in alcohol. It is best administered in the form of simple aqueous solution. The saline taste may be disguised with syrup.

Potassii Citras.—Potassium Citrate, U. S. P. It should contain not less than 99 per cent. of pure potassium citrate ($\text{K}_3\text{C}_6\text{H}_5\text{O}_7 \cdot \text{H}_2\text{O}$). It occurs as transparent crystals or a white granular powder, odorless and having a cooling, saline taste; deliquescent on exposure to air. It is very soluble (1:0.5) in water but only slightly soluble in alcohol. It is best administered in the form of a simple solution with water or as an effervescent draught.

Potassii Citras Effervescens.—Effervescent Potassium Citrate, U. S. P. A mixture of potassium citrate 20 per cent. with sodium bicarbonate, tartaric acid and citric acid. This product must be kept in well-stoppered bottles. It may be administered in doses of 4 gm. (60 grains.)

* The materia medica of other diuretics will be found under other groups to which they also belong.

DIAPHORETICS

One of the functions of the sweat glands is to provide moisture, which by its evaporation cools the body, the secretion of sweat being increased when the production of heat by the body is increased.

This secretion is controlled largely by the heat regulating centers, and when the blood flowing through the carotids is warmed it causes an increased secretion, as does the warming of the surface of the body also.

The activity of the sweat glands is influenced less by the blood supply than is that of most of the glands of the body, and profuse sweating may occur when the skin is pale, and, on the other hand, there may be little secretion when the skin is flushed and hot in fever. However, heat increases the excitability of the nerve endings in the sweat glands and an abundant supply of blood often promotes the secretion.

The composition of the sweat and the daily amount secreted varies widely under normal conditions, and still more widely under pathologic conditions.

The amount of sweat secreted in twenty-four hours by a healthy man with light exercise probably does not often fall below 500 c.c. (1 pint), but with hard work during hot weather the secretion may become more than ten times as active, and under pathologic conditions, as during sudden collapse, the amount secreted in a few minutes may equal the amount which is secreted in an entire day under ordinary conditions.

The sweat contains small amounts of salts, of which sodium chlorid constitutes much the larger part, and usually only insignificant amounts of organic matter, but when the activity of the glands is greatly increased, during severe muscular exercise or by hot vapor baths, the amount of organic matter is increased notably, and when the kidneys become incapable of secreting urea as fast as it is formed, so that it accumulates in the blood, a considerable amount is found in the sweat, and it is commonly stated that crystals of urea sometimes may be found on the skin under those conditions.

It seems probable that one of the functions of the sweat glands is to provide a means of eliminating water from the blood without a corresponding loss of its salts, but when the loss of water from the blood is made up by absorption either from the gastrointestinal tract or from the tissues, the loss of salts may be important, and the blood may then have a lower concentration than before active sweating was induced. From this it would seem that the sweat glands supplement the action of the kidneys to an important degree at times.

Sweating also serves to remove large numbers of bacteria from the deeper layers of the skin, and it is probable that with the profuse sweating of exercise that this action is not without importance.

The methods of inducing active sweating without the use of drugs do not call for discussion in this place; the actions of the analgesic antipyretics and various vasodilators have been discussed elsewhere.

PILOCARPIN

Pilocarpin stimulates all parasympathetic nerve endings and the sympathetic nerve endings in the sweat glands, which, as previously stated, behave toward several drugs like the parasympathetic.

The sweating begins in about fifteen minutes and lasts about two hours. The stimulation of the chorda causes profuse salivation, while the secretion of the bronchial glands may embarrass respiration, and pilocarpin is therefore contra-indicated in patients in whom there is a predisposition to edema of the lungs.

Pilocarpin stimulates the vagus endings, causing moderate slowing of the heart rate, but the action differs essentially from that of digitalis, for the stimulation resulting from small doses tends to pass into depression so that the heart rate increases, and when large doses have been administered the stimulation is brief and the depression almost as great as that resulting from atropin. Hence it is impossible to induce an important degree of slowing of the heart by doses of pilocarpin.

The toxic actions of pilocarpin on the central nervous system are exerted mainly on the medulla.

Eggleston (personal communication) found that the intravenous injection in the dog of doses corresponding to 45 mg. ($\frac{3}{4}$ grain) for a man caused vomiting through the action on the center, and that the emetic action of very much larger doses could be prevented by the injection of atropin in amounts equal to less than one one-hundredth of that of the pilocarpin used.

Nausea and vomiting are commonly accompanied by a flow of tears, saliva and sweat; in the case of pilocarpin, the effect is augmented by the stimulation of the nerve ends in the glands.

Diarrhea is also a symptom of poisoning with pilocarpin, the action being partly peripheral and probably partly central, since many drugs that stimulate the vomiting center in the medulla also cause diarrhea through their central action.

The respiration is increased at first, and later there is depression of the respiratory and vasomotor centers; but when death results, it is probably secondary to the pulmonary edema, even in those cases in which the heart actually stops before the respiration.

The action of physostigmin resembles that of pilocarpin qualitatively, but it is so much more depressant than pilocarpin to the central nervous system in doses producing an equal diaphoretic effect that it is never used for that purpose.

THERAPEUTIC USES

Sweating serves to increase the concentration of the blood, thus promoting the absorption of dropsical effusions if the amount of water ingested is restricted sufficiently.

Profuse sweating serves to remove a certain amount of various substances which are usually excreted by the kidneys, and while the amount of nitrogenous matter normally excreted in the sweat during rest is insignificant, a much larger amount is excreted during profuse sweating.

The amount of urea eliminated during even profuse sweating would seem to be too small to account for the improvement which results from sweat baths in *nephritis* and *uremic poisoning*, hence one cannot say

to what the improvement is attributable. It is possible that the removal of chlorids from the blood may relieve the kidney, for, as previously stated, sodium chlorid is actually injurious to the kidneys under certain circumstances.

It is popularly supposed that other toxic substances are excreted in this way, but our knowledge of this subject is very imperfect.

A popular treatment of "colds" consists in the use of large quantities of hot lemonade while the body is kept warm to induce sweating. A hot mustard foot bath is commonly taken at the same time, and this treatment frequently results in the disappearance of the symptoms, probably because the alteration in the distribution of the blood which is induced relieves the local congestion.

The same objects are often accomplished by the use of the compound powder of ipecac and opium and the mustard foot bath, or by a hot bath taken just before retiring in a warm room; this induces active sweating which continues for some hours, if the patient is kept warmly covered.

Chronic rheumatism and gonorrheal arthritis are often treated by placing the affected limb in a hot-air chamber for half an hour, while maintaining a temperature of from 70 to 90 C. (150 to 180 F.).

A limb, or even the whole body except the head, may be subjected to a high temperature for a short time if care is taken to provide for a sufficient circulation of air to insure the evaporation of water as fast as it is eliminated in the sweat. Heating a limb or the body causes the body temperature to rise—sometimes as much as several degrees—and cold water or an ice bag should be applied to the head to prevent the effects on the brain which would ensue.

Solution of ammonium acetate and spirit of nitrous ether are commonly used as diaphoretics during fevers, but their action is feeble, and we have many better means of inducing sweating.

Pilocarpin is used as a diaphoretic in certain diseases of the skin, and it is generally credited with the property of stimulating the growth of the hair, but

failure is far more common than success when it is used in baldness.

Doses just short of that required to induce sweating are sometimes used to relieve itching in generalized acute eczema, urticaria and other conditions. Its use as a miotic has been discussed.

Pilocarpus owes its therapeutic effects to the pilocarpin which it contains, but it would seem that there is never any occasion to use the crude drug rather than pilocarpin.

DOSAGE

The diaphoretic dose of the compound powder of ipecac and opium is 0.6 gm. (10 grains); the dose of the hydrochlorid or nitrate of pilocarpin is from 0.001 to 0.01 gm. ($\frac{1}{60}$ to $\frac{1}{6}$ grain).

Doses of 5 mg. ($\frac{1}{12}$ grain) of pilocarpin hydrochlorid administered three times a day are said to cause moderate sweating without inducing salivation or bronchial secretion that is so often complained of by patients. This dose may be utilized in chronic renal disease, in which pilocarpin is said to be a most useful drug.

MATERIA MEDICA

The compound powder of ipecac and opium has been mentioned under the morphin group; spirit of nitrous ether under the circulatory depressants.

Liquor Ammoniae Acetatis.—Solution of Ammonium Acetate, U. S. P. This preparation, formerly known as spirit of Mindererus, should be freshly prepared; it is a clear, colorless liquid, free from empyreuma, having a saline taste and an acid reaction. The solution should contain about 7 per cent. of ammonium acetate with small amounts of acetic and carbonic acid.

Pilocarpus.—Pilocarpus, U. S. P. Jaborandi. The dried leaflets of *Pilocarpus Jaborandi* and of *P. microphyllus*. This drug is occasionally used in the form of an infusion or as the official fluidextract, the latter in doses of about 2 c.c. (30 minims). The action of the drug is essentially that of the chief alkaloid, pilocarpin, and as the drug and preparations of it may vary

in activity, the alkaloid is usually preferred. This is official as:

Pilocarpinae Hydrochloridum.—Pilocarpin Hydrochlorid, U. S. P. This salt occurs as colorless, odorless crystals, having a faintly bitter taste. It is deliquescent in moist air and very soluble (1:0.3) in water and freely soluble (1:2.3) in alcohol.

Pilocarpinae Nitras.—Pilocarpin Nitrate, U. S. P. This salt occurs as colorless crystals or a white crystalline powder, having a faintly bitter taste. It is permanent in air and is freely soluble (1:4) in water and soluble (1:60) in alcohol. This preparation is somewhat less soluble than the hydrochlorid and apart from being permanent in air, has no evident advantages over the more widely used salt of the alkaloid.

Both the hydrochlorid and the nitrate may be administered in the form of solution, though they are frequently given in the form of pills or compressed tablets.

CHAPTER VIII.—EVACUANTS

Drugs that are used to cause evacuation of the bowels are variously classified; according to their origin and chemical nature; according to the intensity of their action, and according to their general mode of action. The term laxative is applied to those which cause a nearly normal movement of the bowel, attended with little or no pain; if the action is much more vigorous and several movements are induced, the term purgative or cathartic is employed; and when a large amount of fluid is evacuated with the feces the action is termed drastic, or hydragogue.

For practical purposes it will be convenient to discuss the evacuants with reference to the part of the intestine on which they exert their main action, for a drug may be laxative or drastic, dependent on the dose employed and other conditions, and evacuants must be chosen with strict regard to their mode of action and the seat of this action.

The processes of digestion are so closely related to the intestinal movements that a brief discussion of the physiology of the gastro-intestinal tract is indispensable for a clear presentation of the subject of evacuants.

The stomach is an automatic organ, containing within its walls the plexuses of Meissner and Auerbach, on which its automaticity probably depends; at any rate the surviving excised stomach is capable of maintaining regular movements, and the processes of secretion of gastric juice may take place after the connection with the central nervous system has been severed, but the stomach is influenced both as to movements and secretions, by two sets of nerves from the central nervous system, the parasympathetic (vagus), the functions of which are here mainly motor, and the sympathetic (splanchnic) which is mainly inhibitory. The control of these two nerves is so coordinated that when one of them is stimulated the other is usually depressed.

The functions of the stomach are to secrete the gastric juice and to maintain movements which serve to mix the food with this juice and to drive the digested food into the intestine.

The length of time during which food remains in the stomach varies with the nature of the food, and it may be influenced greatly by drugs. Proteins are digested more slowly than carbohydrates, and fats pass still more slowly into the intestine, and if they be taken before proteins and carbohydrates they delay their passage through the pylorus.

The sphincter of the pylorus relaxes periodically to allow the fluid portions of the stomach contents to pass into the intestine. An alkaline reaction in the duodenum promotes, an acid reaction delays, this relaxation, but when water or a dilute solution of a salt is taken during digestion, it passes along the lesser curvature of the stomach, and reaching the pylorus without mixing with the rest of the stomach contents, passes rapidly into the intestine. This is of some practical importance with reference to the action of certain of the purgatives.

Strong stimulation of the vagus, such as toxic doses of morphin induce, cause spasmodic contraction of the pylorus and the passage of the stomach contents may be delayed indefinitely. Stimulation of the splanchnic causes cessation of the movements of the normal stomach and relaxation of the pylorus, but such stimulation of the splanchnic cannot overcome strong vagus stimulation. In such cases depression of the vagus is more effective, hence atropin is used to lessen excessive movements of the stomach in gastric ulcer. This also serves to explain why large doses of morphin are contra-indicated in that condition, but small doses, sufficient to lessen pain, may be used, for the gastric effects of vagus stimulation are not usually elicited from less than 10 mg. ($\frac{1}{8}$ grain), while half that amount exerts a marked analgesic action.

Atropin is not so effective in quieting the movements of the stomach when these are due to diminished tone of the splanchnic, for then the automatic mechanism alone suffices to increase the activity of the movements and depression of the vagus is then of little

value. Unfortunately, we have no drug which is of much use in increasing the tone of the sympathetic, unless it be ergot.

The mechanism controlling the activities of the intestines is much like that of the stomach. Peristaltic movements in the intestine consist of waves of contraction preceded by relaxation of the musculature of the wall; these are automatic, but they are influenced by parasympathetic (vagus) and sympathetic (splanchnic) nerves.

The function of the parasympathetic nerve to the intestine is mainly motor and that of the sympathetic is mainly inhibitory, as in the stomach, but it seems probable that there are some inhibitory fibers in the vagus, and some motor fibers in the sympathetic. The vagus is distributed to the intestine as far down as the descending part of the colon, where its place as a parasympathetic motor nerve is taken by the erigens, on which atropin and some other drugs act in the same way that they do on the vagus, but less effectively. The nerves which supply the colon and rectum also supply the uterus, which explains in part the effect of certain purgatives on that organ.

Stimulation of the parasympathetic (vagus or erigens) nerve to the intestine causes active peristalsis, and strong stimulation of certain centers in the medulla is followed by diarrhea. The intestinal movements are also subject to psychic influence, but the mechanism of this is not understood. It is possible that the intestinal peristalsis which accompanies certain emotions may be due in part to an increase of carbon dioxid in the blood, this increase being due to respiratory depression, for carbon dioxid and hydrogen sulphid are normal stimuli to the intestine, causing peristalsis.²²

The movements of the large intestine differ considerably from those of the small. The contents of the

22. Certain emotions, such as fear, exert two types of action in different individuals; in one type the effects are referable to stimulation of the sympathetic, and include high blood pressure and inhibition of the gastro-intestinal movements; in the other their effects are referable in part to stimulation of the parasympathetic nerves, and include low blood pressure and active movements of the gastro-intestinal tract.

colon are forced along to the descending part because of overfilling from the ileum, and such movements as occur in the ascending and transverse portions are in the reverse direction, serving to keep the contents thoroughly mixed and promoting absorption. In the descending colon the contents are driven very slowly toward the rectum by means of peristaltic movements much like those in the small intestine. It is uncertain whether the rectum normally contains fecal matter except just before defecation, but there is no reason to doubt that its distention by feces causes a desire to go to stool. The retention of feces in the rectum may lead to dilatation, and the development of a form of chronic constipation.

Anything which increases the bulk of the intestinal contents will promote intestinal peristalsis, for this distention of the intestine seems to be one of the chief stimuli to the automatic mechanism. The fluid contents of the intestine may be increased by augmented gastric or intestinal secretion, or by diminished absorption from the intestine into the circulation.

Estimates of the total amount of fluid secreted by the different digestive organs vary considerably, but it may be accepted that from 3 to 5 liters (from 6 to 10 pints) of fluid are secreted daily by the salivary, gastric and intestinal glands and the pancreas and liver together, and that nearly all of this, together with the liquefied food, enters the small intestine, and a large part of it reaches the colon. From this it is evident why so much fluid may be removed from the body by even a mild, but rapidly acting, evacuant. The composition of the blood can be altered rapidly in this way, and especially by those cathartics which stimulate the intestinal glands to increased secretion. With the changes in the composition of the blood thus induced are associated corresponding changes in the secretions and excretions throughout the body, for most of the glands are influenced profoundly by the composition of the blood, as well as by changes in the amount with which they are supplied.

The passage of fluid through the small intestine requires from eight to twenty hours, as a rule (only a

few minutes in some conditions of hyperexcitability of the intestine), and the passage through the large intestine requires a shorter period, during which active absorption of fluid takes place, leaving the fecal mass composed mainly of bacteria, undigested food particles, such as the lignin of vegetables, detritus of the intestine, and various principles in small amount, together with enough moisture to make it plastic.

If the intestinal movements are unduly sluggish, opportunity is afforded for the absorption of too large a proportion of fluid, the feces become hard, dry and difficult to propel by the normal peristaltic movements, and it becomes necessary to soften such masses before they can be evacuated.

There are various physiologic ways of preventing this sluggishness of the intestinal movements, and it is obvious that such means should be tried before resorting to the use of drugs. The taking of an adequate amount of cold (not iced) water between meals affords the simplest means of hastening peristalsis in the small intestine, and thus indirectly, in the large, for, as previously stated, when water is taken during digestion it passes rapidly into the intestine, and probably even more rapidly if taken when the stomach is empty.

Some stress is placed on the taking of this cold water between meals, rather than with them, for secretion of the digestive fluids depends to some degree on the amount of fluid in the circulation and tissues. If a normal amount of the digestive secretions is available it supplies the fluid which is requisite for normal peristalsis, and it is only when this has been absorbed, at least in large part, that the additional water taken between meals is required to maintain the bulk of intestinal fluid which is required for active peristalsis.

Some stress is also placed on the use of cold water rather than hot fluids, such as tea and coffee, for hot fluids promote rapid absorption from the small intestine and even less fluid will then reach the colon. It seems probable that the constipating effect which tea and coffee often exert is due in part to the fact that the rapid absorption of fluid from the small intestine induces active diuresis, which is further augmented by

the action of the caffeine which they contain, and that this diuresis increases the viscosity of the blood, which in turn diminishes the gastric and intestinal secretions, the increased absorption from the intestine, and the diminished secretion into it cooperating to deprive the intestine of its normal stimulus to peristalsis.

A glass of cold water taken on rising is often sufficient to cause prompt evacuation of the bowels.

Laxatives increase the peristalsis slightly and the feces are evacuated without becoming dehydrated in the colon.

Many persons habitually eat too little, and it is a matter of common observation that one who suffers from mild chronic constipation associated with a spare diet will often have a normal stool soon after taking a large meal. Of course, overeating is not advocated.

It is often urged that a part of the food should not be too readily digestible, and while it is true that indigestible food does promote peristalsis, it does not appear to be necessary, provided that the diet is abundant.

A good appetite, which insures the taking of a fairly large amount of food, and good digestion, which insures the secretion of an adequate amount of fluid in the gastro-intestinal tract, are far more effective in securing active peristalsis than a small amount of indigestible food would be, for undigested food constitutes only an insignificant part of the normal intestinal contents, and furthermore, soft indigestible matter always invites the activity of pathogenic micro-organisms.

An ideal cathartic should pass through the stomach without disturbing it and exert its action on the intestine without causing pain or inflammation, and these conditions must be approximated in order that a drug may be of any use as an evacuant of the intestine.

We are in need of an evacuant which is suitable for subcutaneous injection, and which will then produce purgation without giving rise to excessive irritation at the point of injection, or irritating the kidneys. None of the agents which we use as cathartics is well adapted for therapeutic use by subcutaneous injection, some being local irritants, others having undesired side actions.

Evacuants may be classified conveniently for study as follows: (1) those acting mainly on the small intestine; (2) those acting mainly on the large intestine; (3) those acting on the small and large intestines including alkaloidal evacuants; (4) those acting on the rectum; (5) miscellaneous measures for inducing purgation.

1. EVACUANTS ACTING MAINLY ON THE SMALL INTESTINE

OILS

Neutral fats and saponifiable oils like butter and olive oil pass practically unchanged through the stomach, but are saponified more or less completely in the small intestine, and the resulting soaps may be sufficiently irritating to the intestinal mucous membrane to cause increased peristalsis and with an excess of the fat or oil act as a mild laxative.

Castor oil, which consists largely of ricinolein, yields a soap that is much more irritating and prompt in its action. The direct influence of the irritation is usually limited wholly or mainly to the small intestine, because these soaps are absorbed into the circulation without reaching the colon. The increased peristalsis in the small intestine rapidly drives a large amount of fluid into the colon, distending it and causing an evacuation before the stools become fully formed, or at least while they are still soft, because a sufficient interval of time is not afforded for as much fluid to be absorbed as usual.

Castor oil acts mildly even in fairly large doses, because the ricinoleic acid is liberated slowly, and the more active the peristalsis the less is the time allowed for the further liberation of the acid, hence, to a certain extent, its action is self-limiting.

Croton oil contains some free crotonoleic acid, which is irritant to the body tissues, hence it irritates the throat and stomach unless measures are taken to prevent it, and it may give rise to nausea and vomiting. It is decomposed in the small intestine, with the formation of crotonoleates. These are far more actively

irritating than the ricinoleates, and croton oil causes more violent peristalsis than castor oil, but it may induce intestinal inflammation without purgation.

THERAPEUTIC USES

Castor oil is used frequently for children, being a dependable laxative or purgative which may be administered without fear of causing intestinal inflammation or disturbing the stomach seriously, but it is not suited for continued use in chronic constipation because of its gradually lessening effect. It is also applied to the skin and to the eye as a demulcent.

Croton oil finds its special field of usefulness in mania and coma, when a prompt evacuation of the bowels is desired.

Its irritant action in the stomach, and the possibility of its causing severe intestinal inflammation limit its use as an evacuant to those cases in which the administration of a rapidly acting drug in small amount is necessary.

DOSAGE

The dose of castor oil is 15 c.c. (4 fluidrams). The taste is disagreeable, and children manifest an especial repugnance for it, so that it is best administered in such a way that the taste is masked.

Because of its disagreeable taste castor oil is given preferably with pungent, freely frothing beverages, or enclosed in soft gelatin capsules holding about 1 teaspoonful. It may also be administered in the form of a mixture or emulsion and this latter type of administration is becoming popular. The following may be used as a type formula:

	gm. or c.c.	
Benzosulphinid (saccharin).....	0 05	1 grain
Oil of Cloves.....	0 2	3 drops
Oil of Cinnamon.....	0 3	5 drops
Alcohol	4 0	1 fl. dram
Castor oil, a sufficient quantity		3 fl. ounces
to make	100	

In making this mixture, the benzosulphinid, oil of cloves and oil of cinnamon should be dissolved in the alcohol and this in turn added to the castor oil.

The dose of croton oil is 0.05 c.c. (1 minim). It may be administered in drop doses placed well back on the tongue, in the form of a pill made with bread-crumbs or other absorbent, or diluted with a bland oil and given in a gelatin capsule, or simply dropped on a small lump of sugar, which should be swallowed quickly.

MATERIA MEDICA

Oleum Ricini.—Castor Oil, U. S. P.—A neutral fatty oil obtained from the seeds of *Ricinus communis* and having the property of being miscible with alcohol in practically all proportions. When well washed, castor oil is colorless or slightly yellow with practically no odor, but because of its viscosity and slightly acrid taste is not readily swallowed.

Oleum Tiglli.—Croton Oil, U. S. P.—This is a fatty oil expressed from the seeds of *Croton Tiglium*; it varies in color from pale yellow to brown. Like castor oil it is soluble in alcohol, the degree of solubility increasing with age and the nature of the resulting decomposition. Croton oil is frequently adulterated and a pure oil is probably not now obtainable.

RESIN ANHYDRIDS

There are many vegetable drugs which contain glucosidal acids, or anhydrides, which induce purgation in much the same way that castor oil and croton oil do. The drugs of this group, as a rule, are only slightly irritant to the stomach, but they become much more actively irritant in the presence of bile and when they reach the intestine cause increased peristalsis. The action of small doses is limited to the small intestine mainly but large doses often cause gastric irritation, with nausea and vomiting, and in addition to the effect on the small intestine some of the drug passes into the colon, causing pain, tenesmus and watery evacuations. Very large doses may cause bloody stools, collapse and even death. Moderate doses of these drugs cause little or no pain, but active peristalsis in the small intestine is accompanied by sounds and sensations due to the movements of fluid and gas.

THERAPEUTIC USES

All the members of this group except podophyllum and its resin are used to secure prompt evacuation of the bowels, and all of them are capable of causing profuse watery stools. Their actions are quite similar, differing only in minor details, hence it is often a matter of no great importance which of the drugs of the group is used in a given case.

They are used for the removal of fluid in dropsical conditions, especially as a preliminary to the use of digitalis and other drugs which promote diuresis. They were formerly used much more for this purpose than at present, and many physicians have abandoned their use in this way because of the dangerous depression which they sometimes cause in those suffering from cardiac diseases, and in asthenic and anemic patients.

These drugs, in doses sufficient to cause watery stools, remove fermenting and putrefying material, as well as bacteria, from the intestinal tract, and repeated catharsis may render the bowel almost sterile for a time perhaps, but large doses of such irritants may injure the natural protective powers of the intestine against bacteria and permit the latter to grow more rapidly than before.

Colocynth extract, resin of jalap or elaterin may be used for the removal of poisons which have passed through the stomach into the intestine, especially when the poison has been taken in a slowly absorbable form (belladonna berries). The action of podophyllum is usually elicited too slowly for this purpose.

The severe irritant action of these agents contraindicates their use in the presence of severe inflammation of the intestine, and large doses are contraindicated in menstruation and in pregnancy, but small doses have practically no effect on the uterus, and may be used without fear of inducing miscarriage or abortion.

The resin anhydrides are sometimes used for the removal of hard dry masses of feces which have been allowed to accumulate in the colon, because of the large amount of water which they drive into that organ. It is more rational to administer a suitable enema when such masses are to be softened, because they do not

take up liquid rapidly, and even violent peristalsis may be insufficient to force them through the anus if they are formed into large masses.

Different members of this group have been recommended for the treatment of chronic constipation, and while they are useful at times, it should be remembered that constipation is a symptom of some other condition. It is better to determine the nature of the cause and direct one's efforts toward relieving it than to use the same method of treatment in every case because of the presence of a single symptom. It is impossible to enumerate here any considerable number of the causes of chronic constipation, but it is probable that its ultimate cause may be found in any one of a large number of habits, or minor derangements of various organs. It has been explained that the diuretic action of tea and coffee may augment chronic constipation by increasing the viscosity of the blood; excessive sweating may do this also. The habitual taking of an insufficient amount of water between meals is a common cause, and at least six glasses of cold water should be taken during the day in addition to any liquid that may be taken at meals. An even larger allowance should be taken if one drinks much tea and coffee, provided that this causes diuresis; or if one sweats a great deal. One is apt to suppose that any loss of water from the body in the urine and sweat is quickly made up through the amount taken for the relief of thirst thus induced, and while this is ultimately true, the amount of water in the circulation and tissues varies quite considerably from hour to hour.

An insufficient, or poorly regulated diet, is probably the commonest cause of chronic constipation, even the value of open air exercise being due largely to the increased appetite, as well as to the improved circulation and consequent secretion of digestive juices.

The trouble usually lies in the sluggishness of the large intestine, whether this be due to an atonic condition of its musculature, or to the lack of bulk in the contents received from the ileum, but the choice of the remedy may be governed by the necessity of avoiding irritation in that part of the intestine which is the seat

of inflammation; for example, one would not use an irritant to the colon in the presence of appendicitis, even after the symptoms have begun to abate. It is conceivable that muscular atony may be the cause of disturbance in one case, while another presenting much the same clinical picture may be due to some disturbance in Auerbach's plexus.

DOSAGE

Colocynth is not used in substance; the extract is laxative in doses of about 0.03 gm. ($\frac{1}{2}$ grain) and drastic in somewhat larger doses, but nearly all evacuants vary widely in their action on different individuals, and with the same individual at different times. One reason for this is that there are all degrees of inertia of the bowel to be overcome, and just as constipation is due to so many different causes, the dose of any given drug to correct it will vary. It is true, however, that any individual who suffers from chronic constipation, or even from occasional attacks, will usually require approximately the same dose to relieve it at different times. Hence the doses given for the purgatives are approximate only, and the drastic dose for one will be merely laxative for another. In the absence of experience as to the dose required for a given patient it is well to give a small dose at first and repeat it in from four to six hours if necessary, except in the case of podophyllum. Drastic doses are not recommended.

The compound extract of colocynth contains extract of colocynth, aloes, scammony and soap, and belongs to the group which acts on the small and large intestines. It is given in doses of 0.5 gm. ($7\frac{1}{2}$ grains). It is much used in the form of the official compound cathartic pill,²³ which is recommended only for its effectiveness.

The dose of elaterin is 0.005 gm. ($\frac{1}{10}$ grain).

Jalap is seldom used in substance alone, but the dose is stated as 1 gm. (15 grains). The compound powder of jalap, containing potassium bitartrate, acts as a saline, as well as a resin anhydrid.

23. This preparation is a survival of the "shotgun" type of mixtures; there is a rational basis, perhaps, for the employment of two evacuants having different seats of action, but there is no apparent advantage in using together two substances having such similarity of action as colocynth and scammony.

Podophyllum is seldom given in substance; the laxative dose of the resin of *podophyllum* is about 0.005 gm. ($\frac{1}{10}$ grain), the purgative dose is about 0.015 gm. ($\frac{1}{4}$ grain).

Drugs belonging to the group of resin anhydrides are preferably administered in the form of pills or massed and enclosed in gelatin capsules.

MATERIA MEDICA

Colocynthis.—Colocynth, U. S. P.—The pulp of the peeled fruit of *Citrullus Colocynthis*, popularly known as bitter apple, has been used medicinally from the earliest times. It is now used chiefly for making:

Extractum Colocynthisidis.—Extract of Colocynth, U. S. P.—Made by exhausting colocynth pulp with diluted alcohol and evaporating the solvent.

Extractum Colocynthisidis Compositum.—Compound extract of Colocynth, U. S. P.—A complex mixture of extract of colocynth (16), purified aloes (50), cardamom (16), resin of scammony (14), and soap (14).

Elaterinum.—Elaterin, U. S. P.—Commercial elaterin is a more or less variable mixture of principles obtained from elaterium, a substance known to the Greeks and Romans and made now, as then, by sedimentation from the juice of *Ecballium Elaterium*, popularly known as the "squirting cucumber." Elaterium has been dispensed by mistake for elaterin, and this substitution, and the variable composition of the more active official product are probably responsible for the steadily decreasing popularity of the crude drug.

Jalapa.—Jalap, U. S. P.—The dried tuberous root of *Exogonium purga* yielding not less than 7 per cent. of total resin is frequently used in the form of powder, more particularly as:

Pulvis Jalapae Compositus.—Compound powder of Jalap, U. S. P.—A mixture of approximately 1 part of powdered jalap and 2 parts of potassium bitartrate.

Podophyllum.—Podophyllum, U. S. P.—The dried rhizome of *Podophyllum peltatum*, mandrake or May apple, one of the comparatively few widely used drugs

of North American origin, is seldom if ever used in any form except:

Resini Podophylli.—Resin of *Podophyllum*, U. S. P. —This preparation, popularly called podophyllin, occurs as a gray or greenish-yellow amorphous powder and is directed to be made by precipitating a somewhat concentrated alcoholic extract with a mixture of hydrochloric acid and water.

2. EVACUANTS ACTING MAINLY ON THE LARGE INTESTINE

ANTHRACENE DERIVATIVES

The drugs of this group depend for their evacuant action on one or more substances which may be considered as derived from anthracene ($C_{14}H_{10}$) or from a derivative of it called anthraquinone ($C_{14}H_8O_2$), which differs from anthracene by having two CO groups uniting two benzene rings, whereas in anthracene the rings are united by two CH groups. Hydroxyanthroquinone has an OH replacing an H of anthraquinone, and several hydroxyanthroquinones are present in different drugs of this group. Among the most common are di-hydroxy-anthroquinone, or emodin, and tri-hydroxy-anthroquinone, or chrysophanic acid.

Emodin is present in all the crude drugs of this group, it and other closely related bodies being formed by the decomposition of glucosidal bodies which are present in larger amount in the crude drugs.

These hydroxyanthroquinones pass through the stomach and small intestine causing no irritation and exert their specific action on the colon. They cause purgation after the lapse of about sixteen to twenty hours following their administration in most cases.

Small doses cause normal evacuations attended with little or no colic; larger doses cause soft, or watery stools, which may be preceded by severe colicky pains. This irritant action on the colon contraindicates their use in menstruation and in pregnancy, because they induce reflex irritation in the uterus, increasing the

menstrual flow when menstruation is in progress, or tending to cause expulsion of the fetus during pregnancy. It is possible that they also act directly on the nerves supplying the uterus. The action which contraindicates their use during menstruation indicates their employment as emmenagogues when it is desired to institute the flow.

Aloes contains about 10 per cent. of aloin which belongs to the hydroxyanthroquinone group. Aloin is inactive itself but is changed into an irritant amorphous substance in the colon, and on this decomposition product the purgative action depends. The formation of this decomposition product is facilitated by the presence of alkalies and iron, hence aloes and aloin are frequently administered with soap and iron.

Aloes is especially prone to cause uterine contractions, probably because the aloin is absorbed in part and acts directly on the uterus, hence purgative doses of aloes are especially contraindicated in pregnancy, but it is the most frequently used of the group for its emmenagogue action. Aloin, after its subcutaneous injection, is excreted into the large intestine causing purgation, but the injection is painful.

Fresh cascara sagrada contains emodin and also a ferment having an emetic action, but this ferment is gradually destroyed when the drug is stored. It also contains a bitter principle which may be utilized as a tonic but the taste is so disagreeable that many prefer to use a preparation in which the taste is masked, or one from which the bitter has been removed in part.

Rhubarb contains chrysophanic acid and emodin. The chrysophanic acid is quite irritant, but it is absorbed without reaching the colon, hence it does not participate in the typical rhubarb action. The irritant action of chrysophanic acid is utilized therapeutically as an application to the skin in the form of chrysarobin ointment, chrysarobin being a compound of chrysophanic acid. Rhubarb also contains tannin; hence it is astringent in small doses, laxative in large, and the astringency tends to assert itself after the laxative effect has been induced. It sometimes causes nausea



and headache. The aromatics present in the aromatic syrup enhance the astringent effect.

Senna contains emodin, and a bitter resin which is not soluble in diluted alcohol, and which is therefore not present in the fluidextract (or in the syrup which is made from the latter).

PHENOLPHTHALEIN

The action of phenolphthalein is much like that of the other hydroxyanthroquinones over which it appears to possess no very decided advantage; it is capable of giving rise to poisoning when overdoses are used. It is a constituent of many proprietary purgatives.

THERAPEUTIC USES

The evacuants of this group are widely used in small doses as laxatives in the treatment of chronic constipation. Aloes, or aloin and cascara sagrada being especially valuable for this purpose. Cascara often exerts a tonic action on the intestine, permitting of a gradual diminution and stopping of the dose as the intestine regains its normal function.

The irritant action of the drugs of this group is so slight that they may be used in small doses for long periods without giving rise to inflammation, and the colon does not appear to habituate itself to their action, so that the same dose may continue to be effective for years. It is true, however, that with increasing obstinacy of the constipation larger doses are often called for in time, but this is rather from an augmentation of the condition which gave rise to constipation, and not from habituation to the drugs of this group.

Cathartic doses of aloin and aloes are not especially to be recommended, cascara sagrada or senna being preferred in such cases. One of the most effective of the common cathartic mixtures is the old time compound infusion of senna (senna, 6; manna, 12; magnesium sulphate, 12; fennel, 2; water to make 100), which acts on the large intestine and in addition promotes peristalsis in the small intestine by preventing absorption of fluid.

Rhubarb is used in the earlier stages of diarrhea to remove irritating substances and then to check intes-

tinal movements; the aromatic syrup is especially adapted for children.

DOSAGE

The laxative dose of aloes is from 0.03 to 0.05 gm. ($\frac{1}{2}$ to 1 grain), the purgative dose (which is not recommended) is from 0.15 to 0.3 gm. (2 to 5 grains). As an emmenagogue the larger dose is employed. Aloin, or the extract of aloes, is commonly used with extract of belladonna or atropin in the treatment of chronic constipation, but the continued use of atropin even in small doses is not certainly free from objections, and there seems less reason for its use with small doses of these drugs than with the larger ones used for active purgation. The official compound laxative pill, which is practically identical with certain proprietary preparations, contains 0.8 mg. ($\frac{1}{80}$ grain) of extract of belladonna, representing about $\frac{1}{10}$ mg. ($\frac{1}{850}$ grain) of atropin. This dose of atropin is probably without material effect on the intestine when a single dose is taken, but the possibility of its disturbing the digestion when long continued is worthy of consideration. The compound laxative pill also contains strychnin and ipecac. The aloin alone in the form of a pill will often act quite as well as the more complex mixture.

To avoid gastric irritation aloes and aloin are preferably administered in the form of pills or, like the drugs belonging to the group of resin anhydrides, massed and enclosed in gelatin capsules. For making the necessary mass it has long been a practice to use soap or one of the gum resins like myrrh or asafetida which have the additional advantage of being somewhat aromatic.

Typical combinations for pills of aloes are included in the several pharmacopeias, the only objection to them being that they are set formulas instead of being adapted to the case in hand. They serve, however, to illustrate the combinations that have been used.

Aloes may be prescribed somewhat as follows:

Aloes	gm.	gr.
Soap	1.3	20
Mix and make into 10 pills.		

Aloes	1.3	20
Myrrh	0.6	10
Powdered Glycyrrhiza	0.6	10
Syrup a sufficient quantity.		
Mix and make into 10 pills.		
Aloes	1.0	15
Asafetida	1.0	15
Soap	1.0	15
Mix and make into 10 pills.		

The dose of extract of aloes is only slightly smaller than that of the aloes itself, and there are no sufficient reasons for the use of this preparation. The laxative dose of aloin is from 8 to 20 mg. ($\frac{1}{8}$ to $\frac{1}{3}$ grain). Phenolphthalein is given in doses of 0.05 to 0.5 gm. (1 to 8 grains) in capsules of cachets. Larger doses are not to be recommended in case the smaller are not effective. Cascara sagrada is rarely given in substance; the fluidextract and the aromatic fluidextract may be given in doses of 0.6 to 2 c.c. (10 to 30 minims), the smaller dose is for repetition several times daily, the larger dose is given after dinner or at bedtime, preferably so that the action may be induced the next morning. The dose of the extract of cascara sagrada is from 0.1 to 0.5 gm. (2 to 8 grains). One should aim to use the smallest dose which is effective, and reduce this from time to time.

Rhubarb is sometimes used in the form of the powder, or one may obtain the drug in the form of "cubes" or "fingers" which are carried conveniently when it is desired to take several doses during the day. The laxative dose of rhubarb is about 1 gm. (15 grains) or more; with smaller doses—0.1 to 0.3 gm. ($1\frac{1}{2}$ to 5 grains) the bitter and astringent actions only are obtained. The dose of the extract of rhubarb is about one-fourth that of the crude drug. The dose of the aromatic tincture is about 2 c.c. (30 minims) and that of the aromatic syrup about 8 c.c. (2 fluidrams). The cathartic dose of senna is about 4 gm. (60 grains) in the form of powder or infusion. The dose of the compound powder of glycyrrhiza (in reality a preparation of senna) is 4 gm. (60 grains). The fluidextract is given in doses of 2 c.c. (30 minims) and the syrup in doses of 4 c.c. (1 fluidram). This dose of the syrup is only half as active as the dose given of the fluidextract.

MATERIA MEDICA

Aloe.—Aloes, U. S. P.—The inspissated juice of the leaves of *Aloe vera* and of other species of *Aloe* has long been used as medicine and is still one of the more popular and widely recognized drugs. The better grades occur in commerce in two forms: the “livery” or “hepatic” containing crystals of aloin distributed throughout a brown more or less opaque mass and the “vitreous” or “lucid” form which is glossy and shows no distinct crystals even under the microscope, due to fusion of the mass by heat. These forms of the drug are due to the method of preparing it and in no way indicate the source or origin. The West Indian (Curaçao and Barbadoes), South African (Cape and Uganda) and East African (Socotrine and Zanzibar) varieties of aloes occur most frequently in commerce and although the two aloins found in them (barbaloin and isobarbaloin) differ somewhat in chemical constitution, they are practically uniform in their action.

Extractum Aloes.—Extract of Aloes, U. S. P.—This is made by exhausting the drug with boiling water and evaporating the resulting liquid to dryness on a water bath. Because of the large amount of water-soluble material in aloes this preparation has little or no advantage over the drug itself.

Aloinum.—Aloin, U. S. P.—A microcrystalline powder obtained from aloes varying in composition and properties according to the source from which it is obtained. The aloin used in this country is chiefly barbaloin derived from the West Indian variety of the drug.

Rhamnus Purshiana.—Cascara Sagrada, U. S. P.—The dried bark of *Rhamnus Purshiana*, a shrub or small tree growing in Northern California, Oregon, and Washington, is probably the most widely used of all North American drugs. Little is as yet known of the constituents of cascara beyond the fact that the fresh bark is bitter, nauseating and comparatively inactive and that these characteristics are modified on keeping. It is for this reason that the pharmacopeia directs that the bark should be collected at least one year

before being used. The more widely used preparations are:

Fluidextractum Rhamni Purshianae.—Fluidextract of Cascara Sagrada, U. S. P.—Each c.c. of this preparation represents 1 gm. of the bark extracted with approximately 40 per cent. alcohol.

Fluidextractum Rhamni Purshianae Aromaticum.—Aromatic fluidextract of Cascara Sagrada, U. S. P.—Each c.c. of this preparation represents 1 gm. of cascara sagrada, the bitter principle of which has been modified by magnesium oxid and the preparation is aromatized with glycyrrhiza and compound spirit of orange.

Rheum.—Rhubarb, U. S. P.—The dried rhizome of *Rheum officinale* collected principally in China and Thibet where the drug has been used for many centuries. Rhubarb contains two different groups of glucosids, rheotano-glucosids and rheoanthra-glucosids. The drug is used in the form of powder or pieces of the rhizome are directed to be chewed and swallowed. The more widely used preparations are:

Extractum Rhei.—Extract of Rhubarb, U. S. P.—Made by exhausting rhubarb with a mixture of alcohol (8) and water (2), and evaporating the resulting liquid.

Tinctura Rhei Aromatica.—Aromatic Tincture of Rhubarb, U. S. P.—Made by exhausting rhubarb (20), Saigon cinnamon (4), cloves (4), and myristica (2) with a mixture of glycerin (10) alcohol (40), and water (40) to make the required (100) amount.

Syrupus Rhei Aromaticus.—Aromatic Syrup of Rhubarb, U. S. P.—A mixture of aromatic tincture of rhubarb (15), and a trace of potassium bicarbonate (0.1) with syrup (85).

Senna.—Senna, U. S. P.—The dried leaflets of *Cassia acutifolia* (Alexandria Senna) or of *Cassia angustifolia* (Indian or Tinnevely Senna). This drug is frequently administered in the form of an infusion; also in powder form as:

Pulvis Glycyrrhizae Compositus.—Compound Powder of Glycyrrhiza, U. S. P.—A mixture of powdered

senna (18), powdered glycyrrhiza (23.6), washed sulphur (8), oil of fennel (0.4) and sugar (50).

The more widely used fluid preparations of senna are:

Fluidextractum Sennae.—Fluidextract of Senna, U. S. P.—Each c.c. of this preparation represents 1 gm. of the drug extracted with diluted alcohol.

Syrupus Sennae.—Syrup of Senna, U. S. P.—A mixture of fluidextract of senna (25), oil of coriander (0.5), and syrup (to make 100).

Phenolphthaleinum.—Phenolphthalein, N. N. R.—A product of the interaction of phenol and phthalic anhydrid which has long been in use as an indicator in chemical analysis. Phenolphthalein occurs as a white or grayish white crystalline powder that is soluble (1:12) in alcohol but nearly insoluble in water. Acid solutions are colorless; alkaline solutions are bright red.

SULPHUR

It is well known that sulphur acts as a laxative, but the exact mechanism of this action is not known with certainty. It was formerly believed that when sulphur was taken by the mouth it passed the stomach unchanged and that it was partly converted into sulphids in the intestine, these being finally absorbed into the circulation.

This view was supported by the fact that the digestion of sulphur with intestinal mucous membrane results in the formation of hydrogen sulphid.

It now seems more probable that when sulphur is administered to man, it is partly converted into sulphurous acid by the mucous membrane of the intestine, and that the acid causes irritation with hyperemia and increased peristalsis.

When large doses of sulphur are taken, only a small proportion undergoes this change as a rule, and it is possible that the rest forms an insoluble mass which increases peristalsis slightly as any insoluble matter does. Rarely serious symptoms of poisoning have followed the administration of large doses of sulphur, presumably due to the absorption of hydrogen sulphid, but this must be a rare accident indeed.

That traces of hydrogen sulphid are formed in accordance with the older idea is extremely probable despite the evidence against it elicited by recent investigators, since the gas is eliminated by the lungs of those who have taken sulphur, and the elimination in this way is said to constitute one of the objections to its use.

DOSAGE

Sulphur, because of its insolubility and practical inertness, may be administered in liberal doses; 4 gm. (60 grains) being frequently given. It is still used in medicine in the form of the compound powder of *glycyrrhiza* referred to under senna.

MATERIA MEDICA

Sulphur is not volatile at ordinary temperatures, is insoluble in water or alcohol, but is soluble in fats and in ether. It is official in the *Pharmacopeia* in three forms:

Sulphur Lotum.—Washed Sulphur, U. S. P.

Sulphur Praecipitatum.—Precipitated Sulphur, U. S. P.

Sulphur Sublimatum.—Sublimed Sulphur, U. S. P.
—In any of the foregoing forms it should contain from 99 to 99.5 per cent. of pure sulphur.

3. EVACUANTS ACTING ON THE SMALL AND THE LARGE INTESTINES

THE MERCURIALS

The insoluble purgative mercurials, including calomel (mild mercurous chlorid), mass of mercury, (blue mass), and mercury with chalk (gray powder), have little action on the stomach unless their passage through it is delayed; their action on the intestine is mildly irritant, increasing peristalsis directly, and possibly increasing the secretion of the intestinal glands, thereby promoting peristalsis indirectly and causing soft stools with little or no pain, or with larger doses causing watery stools with some colic.

Only a small part of the dose of a mercurial is absorbed when evacuation is induced promptly, but when there is interference with the movement of the intestinal contents the mercurials are absorbed. If there is great interference with the passage of the intestinal contents after a large dose of calomel, or other mercurial salt, diuresis is induced. This interference is sometimes secured by administering opium or morphin with small doses of calomel, but if it occurs after large doses toxic symptoms may result.

Other steps should be taken to induce purgation should one of the mercurials fail to act, except when they are taken for their diuretic action.

The mercurials were long supposed to increase the secretion of bile, but this error arose from the fact that they protect the bile from decomposition by the intestinal flora, and prevent its absorption by hastening its passage through the intestines, so that it appears in the stools if the dose be large enough to cause liquid evacuations. The green color of the stools in such cases is sometimes attributed to bile, but it is probably due to the formation of a sulphid of mercury.

There is much uncertainty concerning the reputed antiseptic action of calomel in the intestine. It does not destroy the bacteria in all probability, or greatly inhibit their growth during their stay in the intestine, but great numbers are removed during the purgation. It is a matter of common experience, however, that the condition commonly called "biliousness" (which does not require further description) is often relieved far more effectually even by a merely laxative dose of calomel, than by other evacuants which act as promptly as calomel. On the other hand, many persons find that headaches which are attributed to the products of intestinal putrefaction resulting from bacterial activity, are relieved quite as well by a quickly acting saline purge as by calomel. This does not disprove the claim that calomel has an especial action in the condition mentioned, for obviously, an active cathartic which sweeps out the intestinal contents with a large amount of water in a very short time must remove undigested and putrefying food and enormous numbers of bac-

teria, and thus give relief, but stress is laid on the fact that a mildly acting dose of calomel or other mercurial, which causes only a soft, not liquid stool, gives decided relief from certain forms of headaches which are not relieved by vegetable laxatives.

Calomel often fails to relieve the diarrhea of infants which is caused by bacterial activity, but this does not prove that calomel is not bactericidal. The hypersecretion of mucus in such conditions affords excellent opportunities for the multiplication of bacteria after the calomel has passed through the intestine, and it is not feasible to keep the entire intestinal canal supplied with the drug, since so much would have to be used that systemic poisoning would ensue.

Calomel is more useful in preventing the development of the severe symptoms when taken in time, than in curing them after full development.

Mercury with chalk is less irritating than calomel; the chalk is said to interfere with peristalsis sometimes.

Calomel has little action on the uterus, and moderate doses are therefore not contraindicated in pregnancy. The action of blue mass is much like that of mercury and chalk.

THERAPEUTICS

The therapeutic indications for the use of the mercurial purgatives is sufficiently indicated in the discussion of their actions. Calomel, blue mass or mercury with chalk may be used when there is need for a mild laxative, or in somewhat larger doses when a cathartic is required. Headache due to intestinal putrefaction, the condition called "biliousness," putrefactive diarrhea, and in fact any condition attended with intestinal putrefaction, may serve as an indication for one of the mercurial purgatives unless there is a specific contraindication for their use.

DOSAGE

Calomel was used formerly in enormous doses for a variety of conditions and salivation was a common result, but with a more rational and more limited use of the drug this condition is now rare.

As a result of the reaction following the use of such large doses of calomel physicians went almost to an opposite extreme, and minute, but frequently repeated doses came into favor. If one desires to use such small doses from 3 to 5 mg. ($\frac{1}{20}$ to $\frac{1}{10}$ grain) may be given every fifteen minutes until ten doses are taken. This method of administration sometimes induces nausea without any apparent advantage in the action, but it is possible that it secures a more prolonged, or more frequently repeated, antiseptic action in the intestine.

A dose of from 30 to 60 mg. ($\frac{1}{2}$ to 1 grain) will often act as a laxative after from eight to twelve hours, but it is preferable to give a saline laxative about four to six hours after administering the calomel unless purgation has taken place. Doses of from 0.15 to 0.30 gm. ($2\frac{1}{2}$ to 5 grains) of calomel induce severe purgation with copious watery stools attended with severe griping and a considerable degree of nausea, but such doses have little advantage over smaller doses followed by a saline purgative which causes an equally active purgation with much less discomfort.

From 8 to 15 ($\frac{1}{8}$ to $\frac{1}{4}$ grain) of calomel given to a child at the beginning of an attack of diarrhea, and followed by doses of 5 mg. ($\frac{1}{10}$ grain) twice a day for several days, will often avert more serious symptoms.

It is probable that doses of calomel larger than 0.12 gm. (2 grains) are never required for an adult; should this fail to cause purgation dependence should be placed on other evacuants, particularly the salines.

Sodium bicarbonate is commonly added to calomel under the mistaken idea that it is necessary to administer an alkali with the mercurous salt to prevent its conversion into a mercuric salt by the gastric juice. The amount of sodium bicarbonate usually employed is wholly inadequate to neutralize more than a small part of the gastric juice in the stomach, and no such change takes place when calomel is subjected to the action of the gastric juice without neutralization.

Mass of mercury or mercury with chalk may be given in doses of 0.25 gm. (4 grains).

MATERIA MEDICA

Hydrargyri Chloridum Mite.—Mild Mercurous Chlorid, U. S. P.—Calomel occurs as a heavy, white, impalpable powder that is odorless, tasteless and permanent in air. It is practically insoluble in water, alcohol or ether but undergoes slow changes when exposed to light or when brought in contact with alkalis, acids or decomposable salts. The official substance should contain not less than 99.5 per cent. of mercurous chlorid, HgCl , and should be free from mercuric chlorid and other soluble impurities.

Massa Hydrargyri.—Mass of Mercury, U. S. P.—Popularly known as “blue mass,” this preparation is a mixture of mercury (33) with powdered glycyrrhiza (10), powdered althea (15), glycerin (9), and honey of rose (to make 100). It occurs as a homogeneous, bluish mass which may be readily formed into pills.

Hydrargyrum Cum Creta.—Mercury with Chalk, U. S. P.—This preparation, popularly known as gray powder, occurs as a light gray, rather damp, powder made by thoroughly mixing mercury (38), clarified honey (10), and prepared chalk (57) with enough water to moisten the mass, and then shaking until the globules of mercury are no longer visible under a low power lens. The mixture is subsequently dried and powdered.

SALINE EVACUANTS

When a concentrated solution of one of the slightly diffusible salts is taken into the stomach it becomes diluted with the gastric secretion, or, if the stomach was previously empty, it withdraws fluid from the cells of the stomach, causing irritation, with nausea and vomiting at times.

The rate at which this dilution in the stomach occurs in the absence of a sufficient amount of fluid previously present, will depend to a considerable degree on the relative amount of fluid in the blood and tissues. If they contain an abundance of water, secretion will be active as a rule, and when the solution of the salt has become fairly dilute it will pass into the intestine, but if the blood and tissues contain relatively little

water gastric secretion is slow and nausea and vomiting may result. This is best illustrated by the protocols of two laboratory experiments (hitherto unpublished).

Two dogs, A. and B., received an equal amount of sodium sulphate. Dog A. received the salt in concentrated solution after having been deprived of water for twenty-four hours, and vomited within about five minutes; he even refused water owing to nausea, but when enough water was passed through a tube into his stomach to dilute the salt somewhat, he drank water almost immediately. Dog B. was given the same amount of salt in dilute solution after having had the usual allowance of water; he showed no signs of nausea, and ate food at once (showing absence of nausea).

When a solution of salt has passed into the intestine it retains its water of solution until its concentration has been so reduced as to be approximately equal to that of the blood, the distention of the intestine by the fluid causing peristalsis, the action being exerted in the small and large intestine.

The salts of this group are not absolutely non-absorbable, and when peristalsis is prevented by any means the solutions may be absorbed into the circulation completely. If the absorption takes place, as it always does to some slight extent, the salt is excreted by the kidney, and it may induce diuresis if the absorption has been sufficiently rapid, for the renal epithelium, in marked contrast to that of the intestine, is readily permeable to most of these salts.

Occasionally, large doses of magnesium sulphate have been absorbed in pathologic conditions of the bowel more rapidly than they could be eliminated by the kidney, and have given rise to symptoms of poisoning, and in a few instances death has followed, but this accident is not to be feared except when obstruction of the intestine exists, and, of course, no purgative should be given in such conditions.

When magnesium sulphate (Epsom salt) is absorbed rapidly, or is injected intravenously, in sufficient amounts, it depresses the nervous system and induces complete narcosis with muscular relaxation. The depressant action following the subcutaneous injection is now being utilized in the treatment of the *chronic form* of tetanus with reported success. The

absorption from the intestine is probably too slow in any case to induce serious poisoning unless the kidneys are diseased or marked depression of the central nervous system previously exists. The other purgative salts are devoid of toxic actions after absorption. Magnesium citrate should be open to the same objection as the sulphate, but no cases of poisoning have been reported after its use, so far as we are aware.

The precise mechanism of the purgation induced by these salts is not understood fully, but there is no reason to doubt that their action results largely from their capacity for retaining water and thus distending the bowel. This also explains why concentrated solutions require so much longer time than dilute before causing purgation, and twenty hours may elapse before their effect is induced, whereas dilute solutions are commonly effective within three hours.

The purgative salts have a disagreeably bitter taste, and not infrequently concentrated solutions are taken in order to lessen the time required to drink them; when they are taken in this way a glass of water should be taken immediately to dilute them in the stomach, unless the removal of an excess of water from the tissues is the object in view, in which case concentrated solutions are usually employed. In such cases, gastric irritation may be avoided by taking small amounts of the solution at short intervals.

It is probable that moderately dilute solutions would be more serviceable in such cases than the concentrated ones commonly used. The amount of fluid which can be removed by purgation is very much greater than that required for the moderate dilution of the salt, and the absence of gastric disturbance and the much more rapid effect of the dilute solutions suggest that they might be employed even in dropsical conditions.

Magnesium sulphate is partly converted into carbonate in the intestine, and the liberated sulphuric acid combines with the alkalies which are absorbed and excreted in the urine; thus depriving the body of them. This becomes a matter of importance when the salt is administered continuously for some time, and it is customary in such cases to administer sodium bicarbonate to make up the deficiency. This loss of alkali

does not occur with the use of sodium sulphate or the other purgative salts.

The administration of the sulphates (Epsom salt or sodium sulphate) is followed by the formation of some hydrogen sulphid in the small intestine, and this may give rise to discomfort, with rumbling.

The insoluble magnesium carbonate and the oxid, or calcined magnesia, are partly converted in the stomach into the soluble chlorid, and in the small intestine partly into the soluble bicarbonate. Should they fail to undergo the change they do not cause purgation, and an accumulation of the insoluble carbonate may occur after large doses and cause intestinal obstruction.

Magnesium oxid has an advantage over the carbonate in that it does not yield carbon dioxid gas when neutralized in the stomach. The oxid and carbonate have the advantage over the soluble salts of this group, of being tasteless, and requiring a less bulky dose.

Potassium citrate and bitartrate are absorbed somewhat more rapidly than the other purgative salts, so that small doses induce diuresis without purgation, while large doses cause both, but at best they are only mild laxatives, rarely giving rise to watery stools, but they are active diuretics.

Sodium chlorid or the ordinary table salt in proper dilution is also useful as a laxative and may at times advantageously replace other objectionably bitter salines.

Various acid fruits are mildly laxative, partly because of the citric and malic acids which form citrates and malates in the intestine, and partly because of their cellulose, pectin and sugars which are in part indigestible and absorb liquid, thus increasing the bulk of the intestinal contents in much the same way that the purgative salts do.

THERAPEUTIC USES

The uses of the saline laxatives are indicated largely in the discussion of their actions. They are useful when for any reason a rapid evacuation of the bowels is indicated, as in poisoning by slowly absorbable substances which cannot be removed from the stomach;

to remove bacteria and fermenting masses of food ; to remove dropsical effusions, and in simple constipation.

They have an especial usefulness in that they do not cause irritation when used in dilute solutions.

This would be an appropriate place to discuss the use of purgative mineral waters were it not for the fact that there is no obvious advantage in their use. There can be little doubt that the extraordinary reputation enjoyed by many of these waters depends on the success attained in the treatment of patients at the springs, where special attention is given to all the habits of life, and where only the most pleasant conditions obtain. There is no satisfactory evidence that the ordinary purgative mineral waters have any important action not possessed by a simple solution of the same salts made artificially, and, in fact, many of the mineral purgative waters are more or less artificial, since some are mixtures of waters from different springs while others consist of evaporated spring water, and during the process of evaporation changes occur in the salts present.

Much has been made of the fact that the waters of many mineral springs are radio-active, but radio-therapy is almost wholly in the experimental stage.

One especial advantage which natural mineral waters have over the solutions of purgative salts as they are too often taken is that they are very dilute, and the patient is thus required to take a fairly large amount of water with them. This advantage can be secured so easily, however, by attention to the proper dilution of purgative salts that it is not sufficient to justify the expense of the natural waters.

Magnesium sulphate is largely used in obesity because the magnesium ion combines in part in the intestine with fatty acids which are thus prevented from being absorbed. The tasteless magnesium oxid and carbonate are often used as laxatives in children, especially when it is desired to neutralize the hyper-acidity of the stomach.

The normal sodium phosphate is alkaline in reaction and when it is desired to increase the acidity of the urine the acid phosphate, NaH_2PO_4 , is to be preferred.

or the official di-sodium phosphate may be used adding about three times as much dilute phosphoric acid to it.

A concentrated solution of magnesium sulphate is used as a local application in inflammatory conditions.

DOSAGE

The amount of the several salines required to accomplish a given purpose depends largely on accompanying factors, such as the degree of dilution and the susceptibility of the individual, which vary considerably.

Epsom salt or magnesium sulphate, the effervescent preparation of this substance and sodium sulphate, or Glauber's salt, are usually given in doses of 16 gm. (240 grains) or more, dissolved in from one-half to a full tumbler of cold water. Potassium and sodium tartrate, or Rochelle salt, is given in doses of 8 gm. (120 grains). Sodium chlorid, or ordinary "table salt," and sodium phosphate are given in doses of approximately 4 gm. (60 grains), well diluted with water. The effervescent preparation of sodium phosphate is usually given in double the dose of the simple salt or about 8 gm. (120 grains).

Magnesium sulphate has been used frequently in controlling muscular rigidity in tetanus. One observer reports that he begins with tentative doses of not over 5 c.c. (75 minims), increasing until slight general anesthesia is induced. He reports that as much as 20 c.c. (5 drams) of a 10 or 15 per cent. solution may be injected subcutaneously three or four times daily. He reports that he never saw respiratory failure, but a solution of calcium chlorid is kept at hand. Should the respiration show signs of failure, 5 c.c. (75 minims) of a 5 per cent. solution are injected intravenously.

Magnesium oxid—heavy or light—is given in doses of 2 gm. (30 grains) and the carbonate in somewhat larger amounts, 3 gm. (or 45 grains). Because of the fact that these two substances are insoluble in water they must be administered in the form of mixtures with water or in the case of the heavy magnesium oxid the dry powder can be placed on the tongue and washed down with cold water.

The solution of magnesium citrate is usually dispensed in bottles sufficient for one dose which is drunk as an effervescing draught. Potassium bitartrate, one of the more agreeable of the salines because of its acid taste, is given in doses of 2 gm. (30 grains) mixed with water. Potassium citrate may be given in about the same dose 2 gm. (30 grains) and the effervescent preparation in double this dose—4 gm. (60 grains).

The administration of the salines is somewhat simplified in that their action is enhanced by the presence of water and that, whether water-soluble or not, they are preferably given with copious draughts of water.

MATERIA MEDICA

Magnesii Sulphas.—Magnesium Sulphate, U. S. P.—The official "Epsom salt" contains not less than 97.7 per cent. of pure $\text{MgSO}_4 + 7\text{H}_2\text{O}$. It occurs as small, colorless and odorless crystals that have a cooling, saline and bitter taste. It is freely soluble (1:1) in water but practically insoluble in alcohol.

Magnesii Sulphas Effervescens.—Effervescent Magnesium Sulphate, U. S. P.—A mixture representing magnesium sulphate (50 per cent. crystals) with sodium bicarbonate (40), tartaric acid (21), and citric acid (14). It occurs as irregular granules that should be kept in well-stoppered bottles.

Sodii Sulphas.—Sodium Sulphate, U. S. P.—This salt, popularly called Glauber's salt, should contain 99 per cent. of $\text{Na}_2\text{SO}_4 + 10\text{H}_2\text{O}$, or about 44 per cent. of absolute Na_2SO_4 . This salt occurs in large or small colorless crystals that are odorless and have a bitter, saline taste. It is freely soluble (1:3) in water, but is practically insoluble in alcohol.

Sodii Chloridum.—Sodium Chlorid, U. S. P.—The official salt contains not less than 99 per cent. NaCl . It hardly requires description.

Sodii Phosphas.—Sodium Phosphate, U. S. P.—Di-sodium-ortho-phosphate should contain not less than 99 per cent. of $\text{Na}_2\text{HPO}_4 + 12\text{H}_2\text{O}$, or about 40 per cent. of absolute NaHPO_4 . It may occur in large or small colorless crystals that should be odorless

and have a cooling, saline taste. It is freely soluble (1:5.5) in water but practically insoluble in alcohol.

Sodii Phosphas Effervescens.—Effervescent Sodium Phosphate, U. S. P.—A mixture of exsiccated sodium phosphate (20), sodium bicarbonate (48), tartaric acid (25), and citric acid (16). This mixture occurs in the form of irregular granules that should be kept in well-stoppered bottles.

Sodii Biphosphas. — Sodium Acid Phosphate, N. N. R.—Sodium biphosphate or sodium acid phosphate should contain not less than 82 per cent. of anhydrous sodium dihydrogen phosphate. It occurs as transparent crystals or a white crystalline powder having a saline, somewhat acid taste. It is very soluble in water, but insoluble in alcohol. It is best administered in sweetened water like lemonade. It should not be prescribed in solution with hexamethylenamine.

Magnesii Oxidum.—Magnesium Oxid, U. S. P.—This preparation, which is frequently referred to as "calcined magnesia," occurs in the shops in two forms, the heavy and the light magnesium oxid. In either form it should contain after ignition not less than 96 per cent. of MgO . It occurs either as a bulky, or a dense, fine white powder that is without odor, but has an earthy, not saline, taste. Both forms are almost insoluble in water and quite insoluble in alcohol. The light magnesium oxid unites with water to form a gelatinous hydroxid, differing in this respect from the denser, heavy magnesium oxid. The now widely used magma magnesia or milk of magnesia is a magnesium hydroxid made by precipitating a solution of magnesium sulphate with sodium hydroxid and washing the resulting magma with distilled water to free it of the sulphates.

Magnesii Carbonas. — Magnesium Carbonate, U. S. P.—The official magnesium carbonate is a mixture containing carbonate, hydroxid and water that should yield on ignition, approximately 40 per cent. of

MgO. It occurs in white, friable masses or as a bulky white powder without odor and having a slightly earthy taste. Magnesium carbonate is practically insoluble in water and in alcohol but is soluble with effervescence in dilute acids. In pharmacy it is used chiefly to make:

Liquor Magnesii Citratis.—Solution of Magnesium Citrate, U. S. P.—A solution containing about 10 per cent. of a mixture of neutral and of acid magnesium citrates with potassium citrate and free carbon dioxid. The solution should be freshly prepared when wanted.

Potassii Citras, Potassium Citrate, U. S. P., and *Potassii Citras Effervescens*, Effervescent Potassium Citrate, U. S. P., have been described under the diuretics.

Potassii Bitartras.—Potassium Bitartrate, U. S. P.—This product, popularly known as cream of tartar, contains not less than 99 per cent. of $\text{KHC}_4\text{H}_4\text{O}_6$. It occurs in the shops as a white gritty powder, odorless and having a pleasant, acidulous taste. It is only slightly soluble (1:200) in water and nearly insoluble in alcohol. Potassium bitartrate is one of the ingredients of the compound jalap powder referred to previously.

Potassii et Sodii Tartras.—Potassium and Sodium Tartrate, U. S. P.—Popularly known as Rochelle salt, it contains not less than 99 per cent. of $\text{KNaC}_4\text{H}_4\text{O}_6 + 4\text{H}_2\text{O}$. It occurs as large colorless crystals or as a white powder odorless and having a cooling saline taste. Rochelle salt is freely soluble (1:1.2) in water but practically insoluble in alcohol. Potassium and sodium tartrate is the main ingredient of:

Pulvis Effervescens Compositus.—Compound Effervescing Powder, U. S. P.—This is among the oldest of the effervescing saline draughts; it is popularly designated "Seidlitz powder" and is directed to be dispensed in two papers. The blue paper contains a mixture of sodium bicarbonate (2.5 gm.) and sodium and potassium tartrate (7.7 gm.); the white paper contains tartaric acid (2.1 gm.).

ALKALOIDAL EVACUANTS

PHYSOSTIGMIN

It is apparent from the discussion of the physiology of the gastro-intestinal movements that any drug which stimulates the parasympathetic nerves (vagus and erigens) will cause intestinal peristalsis, or contraction of the muscles of the intestinal walls.

We have a number of agents which stimulate the endings of these nerves, or which increase their excitability to the normal stimuli which reach them through the blood, but these drugs have other actions which usually overshadow their actions on the intestine and prevent their use as evacuants.

Pilocarpin and physostigmin stimulate the vagus and erigens, and induce active movements, not only in the intestine but also in the stomach and uterus. Physostigmin probably acts directly on the smooth muscle of the intestine rendering it hyperexcitable to normal stimuli, and thereby promoting peristalsis. Large doses cause tonic ring-like contractions of the intestine and interfere with the passage of the contents.

Large doses of physostigmin cause violent uterine contractions which may be tonic in character.

There seems to be little reason for the use of any of the pharmaceutic preparations of physostigma, since they contain eseridin and calabar in variable amounts in addition to physostigmin. Eseridin resembles physostigmin in its physiologic actions, but it is weaker, and calabar has a strychnin-like action.

Physostigmin sulphate is hygroscopic and the solution decomposes rapidly with the formation of a ruby-red substance known as red resin. The salicylate is soluble in about 150 parts of water. It is somewhat more stable than the sulphate in solution but it also undergoes the same decomposition.

THERAPEUTIC USES

The actions of physostigmin on the intestine are usually overshadowed by its effects on the central nervous system, and it is far from satisfactory as an evacuant, its use as such appearing to depend rather on

a forlorn hope in the search for a dependable purgative after abdominal operations. The use in man has been encouraged perhaps by the observation that it is a very much more valuable purgative for the herbivora.

The indication for which physostigmin is used as a purgative is atony of the intestine. It should not be used in the presence of inflammation of the intestine or when there is mechanical obstruction. The local and systemic actions of physostigmin are counteracted by atropin in doses of 1 mg. ($\frac{1}{60}$ grain), which may be repeated once or twice if necessary.

DOSAGE

Physostigmin salicylate is used as an evacuant in doses of 1 mg. ($\frac{1}{60}$ grain) and doses of even 2 mg. ($\frac{1}{30}$ grain) are sometimes given, but Sollmann states that such doses are somewhat dangerous, this being especially true in the presence of depression of the central nervous system.

ATROPIN; STRYCHNIN

Atropin and strychnin are never used alone as evacuants, but both of them are added to other substances which induce purgation, and atropin is used to relieve spasm of the intestine which interferes with the passage of the intestinal contents.

Small doses of atropin are said to stimulate Auerbach's plexus, while large doses depress it, and all doses which have any effect depress the parasympathetic (vagus and erigens) endings in the intestine. This is of benefit when overstimulation causes tonic contraction instead of normal peristaltic waves.

There is a possible disadvantage in the long-continued use of even very small doses of atropin which is generally overlooked or disregarded, but which is worth considering. Atropin depresses the vagus endings in all of the organs which it supplies, and even small doses tend to abolish those parts of the gastric, pancreatic and biliary secretions which are under nervous control. It is certain that the minute amount of atropin ($\frac{1}{10}$ mg.— $\frac{1}{650}$ grain) commonly used with aloin in laxative pills has no very pronounced action on these secretions when a single dose is taken, but, on the other

hand, we have no knowledge of the effects of its long-continued use, and in the absence of definite advantages it would be better to omit it when laxative pills are to be taken for prolonged periods.

Strychnin is used in doses of 1 mg. ($\frac{1}{60}$ grain), which are correspondingly larger than those of atropin, and it seems to be useful through its stimulation of Auerbach's plexus.

Extremely small doses of nicotin stimulate, large doses paralyze, the ganglia of the enteric system, and it is a matter of common observation that smoking often promotes peristalsis. Nicotin is not used therapeutically, however, for this purpose.

4. EVACUANTS ACTING ON THE RECTUM

Irritation of the rectum reflexly induces peristalsis in the colon and leads to evacuation of the feces. This rectal irritation may be induced in various ways, the simplest method being a form of local irritation by means of a suppository of soap or glycerin, the injection of a small amount of glycerin or distention by the injection of cold water, or warm water to which soap, glycerin, or other mild irritant, has been added.

If constipation is the result of sluggishness of the movements of the colon, the moderate distention of the rectum by cold water alone will usually suffice to cause a normal evacuation. When the feces have become hard and dry through absorption of an undue amount of their fluid, the normal peristaltic movements are insufficient to drive the intestinal contents along, especially if these have become aggregated into large masses, and the addition of soap to the warm water which is injected slowly, and in sufficient amount so that it penetrates into the colon, aids in softening the masses so that they become at once more plastic and more slippery, and then the peristalsis which is induced by distention of the rectum will suffice to evacuate them.

It is probable that a tube cannot be passed through the rectum high into the colon, but if the fluid be injected slowly and with very slight pressure—not more than that exerted by holding the reservoir a foot

above the recumbent patient — it will pass gradually into the colon, and may even find its way into the ileum.

Daily stools do not invariably prevent the accumulation of such dry, hard masses of fecal matter, for the colon is so voluminous that soft feces may be forced past such masses which gradually increase in size until they finally obstruct the entrance into the rectum, and cannot be evacuated until they are softened or otherwise broken up.

A warm 5 per cent. solution of sodium sulphate is preferable to water alone for such an enema, because the salt delays the absorption of the water, and permits it to act on the fecal masses for a longer time than it would otherwise.

Glycerin is irritant through its capacity for withdrawing water from the tissues. When introduced into the rectum it sets up peristalsis almost at once by reflex action on the colon. It may be injected in pure form, or added to water or used in the form of a suppository.

Soap may be added to warm water to increase its irritant action on the rectum, or to soften fecal masses as just mentioned, or it may be used in the form of a cone, cut from a piece of castile soap and inserted about 2 inches.

Molasses, oil of turpentine and various other irritants are used as additions to warm water enemas, but they do not require detailed discussion.

DOSAGE

Glycerin as such is injected into the rectum in doses of from 4 to 15 c.c. (1 to 4 fluidrams) or used in the form of a glycerin suppository. When used in the form of an enema it is usually added in quantities of from 15 to 30 c.c. (4 to 8 fluidrams) to from 500 to 1,000 c.c. (a pint to a quart) of warm, but not hot, water, to be injected slowly at one time.

Soap enemas are made by dissolving not exceeding 5 per cent. by weight of either hard or soft soap in from 500 to 1,000 c.c. (a pint to a quart) of lukewarm water. Cold water, while often efficient, is not so uni-

formly satisfactory as water at, or slightly above, the body temperature when fecal masses are to be softened.

MATERIA MEDICA

Glycerinum.—Glycerin, U. S. P.—This substance, more properly designated glycerol, is obtained by the decomposition of fats or fatty oils and should contain not less than 95 per cent. of the triatomic alcohol, glycerol. It occurs as a clear, colorless liquid of a thick syrupy consistence, odorless, sweet to the taste and producing a sense of warmth in the mouth, due probably to its great affinity for water. It is miscible in all proportions with water and with alcohol.

Suppositoria Glycerini.—Suppositories of Glycerin, U. S. P.—Each suppository contains approximately 3 gm. (45 grains) of glycerin combined with stearic acid soap.

Sapo.—Soap, U. S. P.—The official soap is directed to be prepared from sodium hydroxid and olive oil and corresponds to what is known in commerce as "pure Castile soap." For use as a suppository a piece of soap is formed into suitable shape and size to weigh approximately 4 gm. (60 grains).

Sapo Mollis.—Soft Soap, U. S. P.—A soap prepared from potassium hydroxid and linseed oil because it is more readily soluble in warm water is frequently used in place of olive oil and sodium hydroxid or hard soap in the making of enemas.

MISCELLANEOUS EVACUANTS

It has been stated frequently that many cases of intestinal stasis or chronic constipation are due to an overdigestion of the food as compared with normal conditions, and that the absence of bulk and necessary moisture retard or otherwise prevent peristalsis.

An effort has been made to overcome these, largely mechanical, factors by the administration of substances which are not in any way affected in the stomach or intestines but which will increase the bulk of the feces, prevent undue absorption of moisture and thus facili-

tate peristalsis. It has long been recognized that certain foods, such as fruits and whole wheat bread, containing a comparatively large percentage of indigestible material, will assist materially in establishing regular habits.

Much the same effect can be obtained by the administration of agar-agar, which has long been used in bacteriologic work as a solidifying material for culture mediums. It is a gelatin-like substance extracted in the East Indies from various seaweeds and has the property of absorbing and retaining water. It prevents the dehydration of feces in the large intestine by holding water tenaciously and thereby serves to increase the bulk of the feces.

Liquid petrolatum or liquid paraffin has long been used to accomplish much the same purpose, though originally it appears to have been given largely with the idea of lubricating the feces. When administered before meals it is mixed with the intestinal material, protecting it to some extent from digestion and preventing the absorption of the contained water.

Lane advised that the heavy Russian mineral oil, or liquid petrolatum, be used to promote the evacuation of the bowels; but Bastedo, who investigated the subject for the Therapeutic Research Committee of the Council, reports that there is no important difference between the actions of the Heavy Russian, and the heavy and light American mineral oils.

The lightest of the American specimens that he investigated had a specific gravity of 0.857 at 22 C., and was markedly fluorescent. All specimens used caused nausea at times, and this was independent of whether the entire dose — from $\frac{1}{2}$ to 3 ounces (15 to 60 c.c.) was given at once or in three parts. The oil sometimes shows a tendency to ooze from the anus between the times of going to stool.

It must be understood that Bastedo's report did not take into consideration many of the very light American mineral oils, such as are commonly used for spraying.

DOSAGE

Agar-agar is given in doses of from 5 to 15 gm. (75 to 240 grains) of the coarsely comminuted substance and may be taken either in water or mixed with food.

Liquid petrolatum should be a colorless and tasteless product, and may be prescribed as "Petrolatum Liquidum Leve" or "Grave," in quantities of from 15 to 30 c.c. (4 to 8 fluidrams) half an hour or an hour before meals, or in larger doses, from 30 to 60 c.c. (1 to 2 fluidounces) on retiring. It is odorless and tasteless and can be taken alone, or, if preferred, a small amount of oil of peppermint may be added to give a distinctive flavor.

CHOLAGOGUES

Cholagogues are agents which stimulate the liver cells, causing an increased secretion of bile. The greater part of the bile which is secreted normally disappears during its passage along the intestine, but various drugs which increase intestinal peristalsis, or which interfere with the decomposition of the bile by bacteria, cause it to appear in the feces in increased amounts, and such drugs were formerly termed cholagogues, though most of them have no action on the liver cells. Later investigations have shown that very few drugs except the salicylates and bile itself have any true cholagogue action.

Bile is partly an excretion, containing such waste products as cholesterin and lecithin, but cholagogues are employed only with reference to the influence of bile in promoting the splitting and absorption of fats in the intestine, or as an adjuvant to the action of certain evacuants, such as aloes. Bile also indirectly promotes the digestion of proteins in the intestine, since unabsorbed fats envelop proteins and interfere with the action of digestive enzymes on them.

The secretion of bile varies with the amount of blood which circulates through the liver, and it seems probable that a hormone present in the blood stimulates the liver cells to secrete bile. The introduction of hydrochloric acid into the duodenum causes an



increased biliary secretion, and it seems probable that this is due to the secretin which is formed from pro-secretin by the acid.

Ox bile, or salts of the bile acids and salicylic acid are the only drugs which are commonly used as cholagogues, and their action is feeble at best.

The appearance of fat in undue amounts in the feces suggests the use of cholagogues, but there are seldom any clear indications for their use in adults, except perhaps as an addition to evacuants.

Cholagogues are contraindicated in the presence of jaundice due to obstruction of the bile ducts.

DOSAGE

The dose of the purified ox bile is 0.5 gm. ($7\frac{1}{2}$ grains), but much larger amounts may be used. It is best administered in the form of pills, or preferably in gelatin capsules which have been treated with formaldehyd to render them less soluble in the stomach.

MATERIA MEDICA

Fel Bovis.—Oxgall, U. S. P.—The fresh bile of *Bos taurus*, used in medicine principally as:

Fel Bovis Purificatum.—Purified Oxgall, U. S. P.—A yellowish-green soft solid, or, more frequently, a yellowish or greenish-yellow powder, having a peculiar odor and a bitter taste. It is prepared by concentrating oxgall and purifying with alcohol. Purified oxgall is very soluble in water or alcohol but is practically insoluble in ether.

CHAPTER IX.—EMETICS, ANTI-EMETICS AND EXPECTORANTS

EMETICS

The first stage of the actions of emetics begins with nausea, salivation, increased bronchial secretion, usually sweating, and often a flow of tears. Great muscular weakness attends this stage and the act of vomiting is usually preceded by increased respiration which then becomes irregular and ceases during the vomiting. Usually the saliva drools from the mouth of animals just before emesis occurs.

Vomiting is accomplished by the coordination of a series of actions which include the following: The pylorus is closed, preventing the passage of the contents of the stomach into the intestine; there are anti-peristaltic movements of the antrum of the stomach, which move the contents into the fundus; the cardia relaxes while the abdominal muscles contract, compressing the stomach and forcing its contents out through the esophagus and the mouth, and sometimes through the nose. The muscles of respiration are fixed, preventing the aspiration of the vomitus.

The reflexes which control the several active movements and inhibitions of the vomiting act are coordinated through a center in the medulla which lies near that of respiration and which is evidently associated with it physiologically. This center is spoken of as the vomiting center, and stimulation of it either directly or reflexly leads to nausea and vomiting. Occasionally the process is arrested before vomiting actually occurs, and the stage of nausea and general muscular depression may then persist for some time.

The fact that vomiting depends on the coordination of reflexes through the central nervous system explains why emesis cannot be induced during narcosis. This must be remembered when it becomes necessary to empty the stomach of a patient who is under the influence of a narcotic such as morphin.

There are two types of emetics: those which irritate the sensory nerve ends in the gastric mucous membrane in a specific manner, whereby vomiting is reflexly induced, and those which act directly on the center without coming in contact with the gastric mucous membrane.

Nearly all drugs which violently irritate the mucous membrane of the stomach cause vomiting unless they also induce narcosis or collapse before the emetic action can be developed, and this coordination of the several actions requires some little time, usually from two to ten minutes. Sensory irritation in the stomach does not always cause emesis, and certain drugs induce nausea and vomiting without causing painful stimuli.

The fact that irritants so commonly cause vomiting has given rise to an unfortunate misconception, and it is frequently argued that a given substance must irritate the stomach directly and induce nausea and vomiting if it is irritant when applied to the mucous membranes of other areas, such as that of the nose or conjunctiva. It is true that a substance may be intensely irritant to the nasal mucous membrane and yet be virtually without action on the stomach. This is precisely what one should expect, for one of the functions of the nasal mucous membrane is to protect the air passages against the entrance of foreign bodies, and it accomplishes this by causing sneezing due to irritation of the nasal mucous membrane, hence the latter possesses a high degree of irritability, but the stomach is frequently subjected to the action of a great variety of irritant vegetable substances, and it has acquired a high degree of tolerance to many of them because its function is to retain ingested material.

Many drugs—perhaps a much larger number than is generally supposed—act directly on the vomiting center. When emesis is the object sought, it may be of less importance to determine the seat of the action than it is in those cases in which it is a side action. We do not know the mechanism of the emetic action of ipecac in full,²⁵ but this does not interfere with our

25. Recent experiments indicate that the action is at least partly central.

employment of it, whereas it is of the first importance to know whether this effect can be avoided by proper methods of administration when it constitutes a side action of a drug which is used for its systemic effects. If such an action is central it can be avoided only by proper regulation of the dosage, and not merely by the choice of the channel by which it is administered.

It is understood that these remarks apply to the usual conditions observed in the more common diseases, and not to those in which the stomach is extraordinarily irritable, for even the sight of food or the odor of a drug may cause emesis in such exceptional conditions, and a drug which would have no effect under ordinary circumstances might then cause nausea and vomiting. A few drugs which irritate the stomach directly are also capable of stimulating the vomiting center when they enter the circulation in sufficient concentration, this being probably true of sodium salicylate, even when it is administered in dilute solution.

Nausea of various grades and emesis are encountered so frequently as side actions that it may be worth while to point out the cause in some of the cases in which it is commonly encountered: Nearly all readily soluble salts either dry or in concentrated solution (from 5 to 20 per cent.), cause irritation of the stomach; this can be avoided by using dilute solutions.

Hydrated chloral is also very irritant to the stomach, and should be administered in dilute solution, and preferably in a bland fluid.

The digitalis bodies without exception, drugs of the picrotoxin group, including wild parsnips, which are frequently eaten by mistake for parsnips, tobacco or nicotin, lobelia, morphin (occasionally pilocarpin) and ergot stimulate the vomiting center directly when overdoses are administered by any channel.

Emetics were used formerly more frequently than they are at present, the stomach tube being employed now in the majority of cases in which it is desired to empty the stomach after poisons have been swallowed, and even after their subcutaneous injection if they are excreted into the stomach, as morphin is. The stom-

ach tube may be used to remove fermenting masses of food, but tenacious curds, undigested meat, and vegetables, not masticated properly, may obstruct the tube, in which case emetics are preferable.

The removal of poisons from the stomach requires the use of rapidly acting emetics when the stomach tube is not available. Emetics are also used to remove foreign bodies from the esophagus and from the upper respiratory passages, and to relieve spasm of the larynx and bronchi in asthma, in nondiphtheritic croup and analogous conditions.

It is frequently stated that emesis may facilitate the passages of gallstones through the bile duct, and it is possible that their action is explainable at least in part by their causing muscular relaxation of the duct.

The nauseant stage of the action of the emetics will be discussed when the expectorants are considered.

It is often stated that emetics are contraindicated after corrosive substances have been swallowed, because of the danger of rupturing the walls of the stomach when they have been weakened by the corrosives, but this danger must be remote in the great majority of cases which the general practitioner is called on to treat. The mechanism of emesis which has been described does not depend on the contraction of the musculature of the stomach alone for expelling the contents, and the contractions of the abdominal muscles serve to compress the walls of the stomach against the contents, but this does not subject them to any severe tension which alone can cause their rupture. Certainly the removal or neutralization of caustics demands action, even though it involves risk.

EMETICS ACTING DIRECTLY ON THE STOMACH

IPECAC

Ipecac contains two alkaloids which contribute to its actions, one of which is of relatively little importance. These are cephaëlin, to which the emetic action is due for the greater part; emetin, which was so named when it was supposed to be the only active constituent present; and psychotrin, which is unimportant.

The different alkaloids of ipecac have not been studied in great detail, and we are not able to determine in every case to which we may attribute a given action of the crude drug.

Emetin is known to be less actively emetic than cephaëlin, but commercial specimens of emetin certainly cause emesis whether they are administered intravenously or by the mouth. Emetin is said to appear in the stomach after its subcutaneous injection, and since it acts slowly after the latter method of administration, we may infer that its action is partly local, but it also stimulates the center directly after its absorption. The alkaloid is also irritant to the skin and to the mucous membranes of the nose and other regions, and when large doses of ipecac are given by the mouth, a portion passes into the intestine and may cause diarrhea.

Emetin possesses a specific action on the ameba of dysentery, and it alone appears to be responsible for the therapeutic effects of ipecac in that disease. It is also actively destructive to the endameba that is said to cause pyorrhea dentalis and pyorrhea alveolaris.

It is said to cause irritation of the intestinal mucous membrane when present in sufficient amount, causing inflammation with paralysis of the capillaries, much as colchicin and arsenic do, the symptoms resembling those caused by arsenic.

Ipecac causes prolonged nausea which is useful when it is employed as an expectorant, but a disadvantage when it is used as an emetic. Moderate doses do not cause such severe depression as antimony.

ZINC SULPHATE AND COPPER SULPHATE

These two salts act on the mucous membrane of the stomach and cause vomiting after a fleeting nauseant stage, and as nearly the whole of the dissolved salt is removed when vomiting occurs, the side actions are brief and of little importance in most cases.

When emesis is delayed or when it fails to occur, after the administration of copper sulphate, the latter passes into the intestine and causes diarrhea, but it is

absorbed very slowly and almost never gives rise to symptoms of poisoning.

Copper sulphate affords one of the best means at our command of combating phosphorus poisoning when that poison is still present in the stomach in solid form. Solutions of copper sulphate deposit an impervious coating of copper on the surface of the phosphorus almost instantly when brought in contact with it, and the rapid emetic action of the antidote serves to remove the phosphorus. The deposition of copper occurs with extreme rapidity even when dilute solutions are used, hence large amounts of dilute solutions are preferable to small amounts of concentrated solutions.

Zinc sulphate causes emesis in the same way that copper sulphate does, and it is equally harmless. The nauseant stage induced by copper and zinc sulphate is too fleeting to permit of their use as expectorants.

Copper sulphate is used for giving a green color to preserved vegetables, and while there is no proof that enough copper can be taken in this way to cause injury, the practice is properly prohibited in the absence of proof that even such small amounts are altogether harmless. It is said that fruits dried in zinc-lined trays contain notable amounts of the metal, but there is no evidence of harmfulness on that account.

The nauseant stage induced by copper and zinc sulphate is too fleeting to permit use as expectorants.

ANTIMONY AND POTASSIUM TARTRATE

Antimony and potassium tartrate, or tartar emetic, acts locally on the gastric mucous membrane to induce nausea and vomiting, but tartar emetic is more actively poisonous when it enters the circulation than are the sulphates of copper and zinc, its systemic effects resembling those of arsenic, but fortunately, the poisonous actions of antimony are seldom observed after its therapeutic use as it is seldom employed except in small doses as a nauseant.

When large doses are taken and vomiting fails to remove the greater part of such a dose, tartar emetic passes into the intestine and causes severe diarrhea

with corrosion of the mucous membranes and absorption into the circulation. In addition to the usual effects which accompany nausea and vomiting, tartar emetic poisoning is attended with copious watery stools, fall of blood pressure, and slow and labored respiration and depression of the central nervous system, ending in collapse and death in rare instances. Some depression of the central nervous system is present even with emetic doses, hence it is not well suited for use in debilitated patients. As little as 0.15 gm. (2 grains) of tartar emetic has caused death when vomiting failed to occur after its administration. When vomiting is delayed for an hour or more after the administration of the usual emetic dose, tannin, lime-water or magnesia should be given to precipitate the antimony and the stomach should be washed, after which active purgation should be induced.

Tartar emetic ointment is irritant, resulting in pustulation, after its application to the skin, the exact mechanism being unknown, though it has been suggested that the double salt is decomposed with the liberation of acid, to which the pustulation is due. Antimony destroys trypanosomes even in dilute solutions. Nauseant doses of antimony are not dangerous.

OTHER LOCALLY ACTING EMETICS

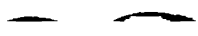
Warm water, slight irritation of the pharynx, as by tickling with a feather, alum, common salt, alkalies (including ammonium carbonate) mustard and numerous other means are employed in domestic practice to induce vomiting through their reflex actions, but these hardly require detailed discussion here.

EMETICS ACTING DIRECTLY ON THE VOMITING CENTER

APOMORPHIN

Apomorphin is the only drug commonly used as an emetic that induces vomiting by its direct action on the medullary center.

When small amounts of apomorphin are injected subcutaneously, nausea and vomiting are induced



within a few minutes, these effects being due to the direct action on the vomiting center in the medulla. Less is required by intramuscular injection, and much less intravenously, to induce the action on the center, but the effects of intravenous administration to dogs are somewhat peculiar in that a definite amount is required—neither more nor less in many cases. If less than the emetic dose is given no perceptible effects are observed; if too much is given depression occurs without emesis, as a rule, and the animal remains refractory for some time. All doses above the minimum effective administered in any other way cause emesis. Much larger doses are required by the mouth than by other channels, and a longer interval ensues before emesis is induced.

In experiments on dogs effective intravenous doses cause emesis within five minutes usually, the emesis is not repeated, and after ten minutes the repetition of the same dose will again produce the same effect as the first. This may be repeated many times with little difference in the effects of the subsequent doses.

Small doses of apomorphin depress the higher centers somewhat as morphin does in animals, depression following very promptly any excitation; but in man the depression of the higher parts of the brain is much less conspicuous, the muscular weakness and other symptoms noted being for the most part secondary to the nauseant action. Cushny states that apomorphin has not caused death in man, though it does occasionally cause collapse.

When small doses are administered the nausea is brief and vomiting occurs but once or twice, but if large doses are used vomiting may be repeated frequently for some time, or there may be prolonged nausea and great muscular weakness without actual emesis, with a slight degree of somnolence.

THERAPEUTIC USES

The therapeutic uses of the emetics have been suggested already in the discussion of this subject, but it remains to point out special indications for the choice of the emetic.

When it is merely desired to empty the stomach of indigestible or fermenting food, the simplest emetic is to be preferred, and warm water, mechanical irritation of the pharynx, warm solution of salt, warm mustard water, or other domestic measures suffice. When prompt results are imperative, as in poisoning, the use of the stomach tube is indicated, but if this is not available a promptly acting and dependable emetic such as apomorphin is required, and the emesis may be made more certain by resorting to accessory means, such as irritation of the pharynx with the finger or a feather, or the use of one of the domestic emetics, such as water with warm salt or mustard, should the apomorphin prove ineffective in a few minutes.

When simple emesis is desired for the purpose of removing indigestible food, copper sulphate or zinc sulphate may be used, and accessory measures may be employed at the same time.

Syrup of ipecac is still used to induce vomiting in children in nondiphtheritic croup, when it is desired to secure relaxation of the laryngeal muscles.

The use of emetics to facilitate the passage of gallstones through the duct would seem to depend, partly at least, on the muscular relaxation which accompanies nausea, and vomiting, and as this muscular relaxation is greater with apomorphin than with the other emetics in general use, probably because of a specific muscular action of the drug, it probably deserves the preference for this purpose, just as it is utilized in overcoming the motor excitement in acute alcoholism, which, being abolished, is followed by quiet or sleep. Apomorphin is also used as a hypnotic in small doses.

Ipecac has been used for many years in the treatment of amebic dysentery, its actions having been variously attributed to its tannin and to its alkaloids. There is no reason to doubt that ipecac owes its value in this condition to its emetin, and since the doses of this alkaloid which are effective in amebic dysentery are not necessarily emetic, the alkaloid has come to replace ipecac largely for this purpose. It may be given orally, intramuscularly or subcutaneously. Hal-

sey recommends the use of pills of ipecac coated with salol, in order that they may pass the stomach undissolved and act on the amebas in the intestine. He calls attention to the fact that the large doses which are required may cause dysenteric symptoms which may be mistaken for the continuance of the disease.

Such large doses are frequently combined with opium to prevent the diarrhea, and to permit the more prolonged action of the alkaloid emetin on the amebas.

The use of ipecac, and especially of emetin hydrochlorid, has been recommended in the treatment of pyorrhea dentalis and pyorrhea alveolaris, which has recently been shown to be extremely common among adults. While emetin is capable of destroying the endameba concerned, reinfection is almost certain to occur unless precautions are taken to prevent it.

Bass and Johns urge that all persons who are now free of the disease should use fluidextract of ipecac as a prophylactic mouth wash. One drop is to be used on the wet tooth brush after cleansing the teeth, and a little of the solution drawn in between the teeth, after which the mouth should not be washed.

The disadvantage of such procedures is that life becomes too burdensome if measures are adopted against every one of the innumerable diseases that threaten us.

DOSAGE

The average emetic dose of ipecac is stated to be about 1 gm. (15 grains); the expectorant dose is from one-tenth to one-twentieth the emetic. It is used in minute doses—about 0.005 gm. ($\frac{1}{12}$ grain) as a gastric sedative.

The initial dose for amebic dysentery is 2 gm. (30 grains) and as this amount will usually cause emesis unless steps are taken to prevent it, it should be preceded by a dose of morphin or opium, or it may be directed to be enclosed in gelatin capsules previously treated with formaldehyd, or made into pills coated thinly with salol. Unless care is taken in coating the pills an overdose of salol will be administered. It is

obviously better to use emetin for amebic dysentery; it should be given in doses of 0.03 gm. ($\frac{1}{2}$ grain).

Copper sulphate and zinc sulphate are given in doses of 1 gm. (15 grains) as emetics. They are not used internally for other purposes.

The emetic dose of apomorphin is 0.005 gm. ($\frac{1}{12}$ grain), injected subcutaneously at intervals of ten minutes until effective, but when used to evacuate poison a somewhat larger dose of apomorphin may be given at once, unless severe depression exists, and emergencies may demand the use of a dose of 0.01 gm. ($\frac{1}{6}$ grain). It is not recommended as an expectorant, but it is sometimes used for that purpose in doses of 0.002 gm. ($\frac{1}{30}$ grain).

The hypnotic dose is about 0.002 gm. ($\frac{1}{30}$ grain) and this or somewhat larger doses may be used subcutaneously in the case of vigorous and violent subjects of alcoholism.

Purves Stewart states that the hypodermic administration of 10 mg. ($\frac{1}{10}$ grain) of apomorphin hydrochlorate will cut short an outbreak of dipsomaniacal drinking (the congenital desire, alternating with the lack of it, or aversion) by bringing on nausea without vomiting, followed by deep sleep lasting from three to eight hours. The hypnotic action is maintained by the administration of doses of from 1 to 2 mg. ($\frac{1}{40}$ to $\frac{1}{30}$ grain) every three hours, if necessary, until three doses have been given.

Nauseant doses of apomorphin suffice, if used during the preliminary stages when there is restlessness.

It is stated that 0.004 gm. ($\frac{1}{15}$ grain) has caused the death of a patient enfeebled by bronchitis, but this must be considered an extraordinary case, and remarkably few deaths have been attributed to it. Apomorphin is practically never given by the stomach to induce emesis, because of the large dose required and the delay in the action.

Antimonials are rarely used for producing emesis at present, but are frequently employed as nauseant expectorants. The emetic dose of antimony and potassium tartrate (or tartar emetic) is 0.03 gm. ($\frac{1}{2}$ grain) but this use is not recommended; the expectorant dose

is 0.001 gm. ($\frac{1}{60}$ grain) which may be repeated every hour, or so often as may be necessary to maintain a slight degree of nausea and its accompanying increased secretion, provided the dose is not pushed to the point of causing severe depression. It is obvious that robust patients can stand repeated doses better than those who are already debilitated.

MATERIA MEDICA

Ipecacuanha.—Ipecac, U. S. P., is described as the dried root of *Cephaelis Ipecacuanha*, commercially known as Rio, Brazilian, or Para ipecac, or *Cephaelis acuminata*, commercially known as Cartagena ipecac. The former variety of this drug is the one that is generally used in European countries and the plant is being cultivated to some extent in Brazil and also in the Straits settlements. The cultivated variety is usually larger than the wild drug of Brazilian origin though in other respects samples of variable origin resemble each other closely. The Cartagena variety comes from Colombia and differs somewhat in appearance from the Rio ipecac and also varies in the nature of its constituents. The drug is described in the United States Pharmacopeia as containing not less than 1.75 per cent. of ipecac alkaloids: a variable mixture of emetin, cephaëlin and psychotrin, which in the drug itself are probably combined with ipecacuanhic acid. Rio ipecac contains about 1.25 per cent. of emetin.

Ipecac is preferably administered in the form of pills, capsules or cachets. The more widely used preparations of the drug are:

Fluidextractum Ipecacuanhae. — Fluidextract of Ipecac, U. S. P.—One hundred c.c. of this preparation represent 100 gm. of ipecac in approximately 75 per cent. alcohol.

Syrupus Ipecacuanhae.—Syrup of Ipecac, U. S. P.—One hundred c.c. of this preparation represent 7 c.c. of fluidextract of ipecac in syrup. It is approximately seven times the strength of the international standard syrup of ipecac.

Emetinae Hydrochloridum.—Emetin Hydrochlorid, N. N. R., occurs as a white crystalline powder soluble in water and in alcohol. It is frequently used in the form of injections and is preferably dispensed in ampules containing from 0.02 to 0.03 gm. ($\frac{1}{3}$ to $\frac{1}{2}$ grain) of emetin hydrochlorid.

Zinci Sulphas.—Zinc Sulphate, U. S. P.—This substance is popularly known as white vitriol. It should contain not less than 99.5 per cent. of pure zinc sulphate, $\text{ZnSO}_4 + 7\text{H}_2\text{O}$. It occurs as colorless, transparent crystals or a crystalline powder without odor and having an astringent caustic taste. It is efflorescent in air and should be kept in well-stoppered bottles. Zinc sulphate is very soluble (1:0.53) in water, but practically insoluble in alcohol. When used as an emetic it should be dissolved in about 50 parts of water.

Cupri Sulphas.—Copper Sulphate, U. S. P., is popularly known as blue vitriol. It should contain not less than 99.5 per cent. of pure copper sulphate, $\text{CuSO}_4 + 5\text{H}_2\text{O}$. It usually occurs in large, deep blue crystals, odorless but having a nauseating metallic taste. Copper sulphate is freely soluble (1:2.2) in water but only slightly soluble (1:400) in alcohol. Like zinc sulphate, it should be dissolved in about 50 parts of water before being administered as an emetic.

Antimonii et Potassii Tartras.—Antimony and Potassium Tartrate, U. S. P., is more frequently referred to as tartar emetic. It should contain not less than 99.5 per cent of the salt, $2\text{K}(\text{SbO})\text{C}_4\text{H}_4\text{O}_6 + \text{H}_2\text{O}$. It occurs as colorless, transparent crystals or as a white granular powder, odorless and having a sweet afterwards disagreeable metallic taste. It is soluble (1:15.5) in water but practically insoluble in alcohol. As an emetic it is preferably administered in the form of a solution like the official wine of antimony which contains 0.4 w/v per cent. of antimony and potassium tartrate.

Apomorphina Hydrochloridum. — Apomorphin Hydrochlorid, U. S. P., is the hydrochlorid of an artificial alkaloid described in connection with morphin. It is soluble (1:40) in water and in alcohol and as

an emetic is usually administered by subcutaneous injection. Solutions decompose readily hence only freshly prepared solutions of crystalline apomorphin hydrochlorid should be used.

ANTI-EMETICS—GASTRIC SEDATIVES

This heterogeneous group, if it can be called a group, of drugs will be discussed briefly. The physiology of emesis which has been discussed in the preceding pages suggests the nature of those agents which may be used to lessen nausea and vomiting, for it is obvious that if emesis results from irritation of the gastric mucous membrane and from stimulation of the vomiting center in the medulla, emollients, demulcents, and other protective agents will lessen the local gastric irritation, and if relief is urgently demanded depression of the central nervous system may be resorted to, though this is seldom necessary, except as a temporary measure, for example, when it becomes necessary to prevent vomiting while administering a drug by the stomach.

Unfortunately, we have no drug which depresses the vomiting center without causing an undesired depression of other nervous centers.

Occasionally vomiting results from reflexes arising elsewhere than in the stomach and other measures than those just mentioned must be employed, for it is well known that foul odors and other purely psychic influences may cause nausea and vomiting. Psychic influences may contribute to gastric disturbances, or may prolong them even when they are not alone sufficient to induce actual emesis, and attention should be paid to such influences.

Heat and atmospheric humidity interfere with digestion and contribute markedly to nausea and vomiting when there may be another exciting cause.

Vomiting occurring after ether anesthesia usually ceases spontaneously after the mucus which has been swallowed is expelled but emesis occurs frequently when food is taken some hours after chloroform anesthesia. Hot water—not tepid—should be sipped, or a glassful may be drunk if small amounts do not give relief.

Cracked ice is sometimes more serviceable than hot water. Thirst following chloroform anesthesia may be relieved by drinking hot water, when it is taken easily, but as this causes diuresis, which may or may not be indicated, and since the taking of rather large quantities of water tends to tax the stomach unduly, rectal injections of warm water may be used to avoid gastric irritation, warm water being retained better than cold.

Infants regurgitate milk without indications of gastric disturbance, when more than sufficient is taken, but when vomiting with distress occurs, due to gastric disturbances, it may indicate the need of substituting barley water for the regular food for a day or two.

When vomiting is secondary to diphtheria it is said to indicate cardiac weakness demanding urgent relief for the heart.

Vomiting occurs in nephritis and disturbances of other organs in which the stomach is not irritated directly, and if the emesis is severe and persistent it may call for sedatives for the vomiting center, in which case morphin may be injected subcutaneously.

Cyclic vomiting has been described as accompanying a variety of symptoms, and is probably not dependent on a single cause. Its treatment cannot be discussed here as the symptoms are too various and these call for separate treatment.

The vomiting of pregnancy often taxes the resources of the obstetrician, and occasionally it cannot be relieved by any means short of terminating the pregnancy. It would be profitless to enumerate all of the drugs which have been suggested for the relief of this symptom, for such a list would be little less than a catalogue of the *materia medica*. Hygienic and dietary measures appear to be the main dependence in such cases. Psychic influences play an important rôle in this condition. Cerium oxalate gained a certain degree of popularity in the relief of vomiting from this and other causes, but there is no evidence that it has any therapeutic value.

Nausea and vomiting which result from indigestion require rest for the stomach, which should be emptied

by washing with a weak alkali if the vomiting does not suffice to remove mucus. A weak solution of sodium bicarbonate may serve the double purpose of dissolving the mucus and causing its removal by vomiting, when there is ineffectual retching.

When there is gastric catarrh, requiring protectives, bismuth subnitrate or subcarbonate may be used; these are preferably administered in the form of powders or mixtures and are not advantageously given in compressed tablets or even in the form of capsules. Acidity may be neutralized by lime-water, magnesia, or by a solution of sodium bicarbonate.

Depressants of the vomiting center include hydrated chloral, morphin and opium, atropin and cocain, and in fact, probably all hypnotics and general anesthetics.

HYDROCYANIC ACID

Hydrocyanic acid may be discussed here, since it is sometimes used to allay nausea; but it is not recommended for that (or any therapeutic use). Its toxicology is of some interest because of the frequency with which it is employed for self-destruction.

Hydrocyanic acid stimulates and later depresses or paralyzes the respiratory center; moderate doses stimulate the vagus center (the endings slightly), causing a slower heart beat. The vessels are constricted and the blood pressure may rise despite the slower heart rate.

The symptoms of poisoning resemble those seen in carbon monoxid poisoning. The latter unites with hemoglobin to form a stable compound that prevents the carrying of oxygen by the corpuscles to the tissues, but hydrocyanic acid acts on the tissues and prevents their utilizing the oxygen that is brought to them.

Hydrocyanic acid is usually absorbed rapidly from the mouth or gastro-intestinal tract, and symptoms of poisoning may occur within a few seconds after it has been swallowed. Fatal doses usually cause death within half an hour, and this may occur within five minutes if a very large dose has been taken.

The symptoms of poisoning with hydrocyanic acid include vertigo, headache, palpitation, dyspnea, con-

vulsions and stoppage of respiration. The heart continues to beat for a time after the respiration ceases.

The characteristic odor of hydrocyanic acid may be detected at necropsy if any remains in the gastrointestinal tract. It is often said that the blood presents a venous appearance after death from this poison, but if death results quickly after a large dose has been taken, the blood may be bright red.

If a patient is seen while a poisonous dose of hydrocyanic acid (or a cyanid) remains in the alimentary tract, the stomach should be emptied as promptly as possible, after which a rapidly acting evacuant (30 gm., 1 ounce of magnesium sulphate in a large tumblerful of water) should be administered.

Hydrogen peroxid, potassium permanganate and sodium thiosulphate (hyposulphite) are said to be useful antidotes to hydrocyanic acid. Since hydrogen peroxid is commonly found in the household, it may be added to the water used in washing the stomach if its use involves no delay. Sodium thiosulphate (4 gm., 60 grains) may be added to the evacuant used after the stomach has been emptied, with a view to forming an innocuous compound with any of the poison that may have passed into the duodenum.

Sollmann advises the subcutaneous injection of 100 c.c. (3 fluidounces) or more of a 3 per cent. solution of the thiosulphate, or the intravenous injection of normal saline with 1 per cent. of sodium thiosulphate. Unfortunately, this antidote will seldom be available in time.

Artificial respiration is indicated if symptoms of severe poisoning develop.

The fatal dose of undiluted hydrocyanic acid is supposed to be about 0.06 c.c. (1 minim), corresponding to 3 c.c. (50 minims) of the official dilute acid, but the activity of the latter varies widely owing to the readiness with which it decomposes.

MATERIA MEDICA

Acidum Hydrocyanicum Dilutum.—Diluted Hydrocyanic Acid, U. S. P., contains 2 per cent. by weight of absolute hydrocyanic acid (HCN). It should be kept in small bottles in a cool place protected from the light.

EXPECTORANTS

The respiratory passages are lined with ciliated epithelium, and normally the secretions of the mucous glands are moved toward the mouth (or anterior nares) by the movement of the cilia, but when the secretions in the smaller air passages become excessive during inflammation, or when they become thick and tenacious, the cilia are incapable of effecting their removal, and coughing is induced. If the secretions become excessively viscid even coughing may be incapable of effecting their removal and it becomes necessary to liquefy them by increasing the secretion of mucus or by means of alkalies.

As previously stated, all nauseants increase the secretion of mucus, hence in practice we choose an agent which has a persistent nauseant action, with a minimum depressant effect on the central nervous system.

Antimony and potassium tartrate is absorbed very slowly from the gastro-intestinal tract, hence small doses suffice to induce prolonged nausea of slight degree, and it is commonly used in the form of a solution or the wine of antimony in the early stages of laryngitis and bronchitis when the secretion is usually scanty and the cough troublesome.

The choice of expectorants is often largely empirical; we do not know whether any of them stimulate the cilia to increased activity or not, and it has been suggested that some of them may act on the smooth muscles of the alveoli and terminal bronchioles in the lungs, increasing their peristaltic movements and forcing mucus accumulations into the bronchi, as the alveoli and the terminal bronchioles are not provided with cilia.

Many salts, including sodium chlorid, ammonium chlorid, and potassium iodid, increase the secretory activity of the mucous glands, effecting the liquefaction of the mucus through the alkalies when these are contained in the secretions, and by diluting these with the increased fluids secreted.

It seems probable that the especial usefulness of ammonium chlorid as an expectorant may depend

partly on the formation of very small amounts of ammonium carbonate in the bronchial mucous membrane, which is especially effective in liquefying tenacious mucus.

A cough which is merely sufficient to remove the secretions from the air passages does not call for treatment, but when there is considerable irritation with frequent coughing while the secretion is scanty, sedatives, such as codein, are indicated. In some cases it is desirable to increase the secretion by means of a nauseant while diminishing the irritation with a sedative to the point that the cough will just suffice for the removal of the secretion.

Patients frequently demand relief from cough when free secretion contraindicates interference.²⁶

Excessive bronchial secretion may be lessened in various ways; atropin depresses the vagus endings in the glands; various volatile oils including the oils of turpentine, of cubebs, and of copaiba are sometimes used, but terpin hydrate has almost completely supplanted the volatile oils for this purpose. Balsam of Peru, benzoin, creosote and other irritants are also used in this way.

Syrup of tolu and syrup of wild cherry are little more than vehicles, the hydrocyanic acid in the latter being present in the merest traces and without therapeutic effect. Hydrocyanic acid was formerly used much more frequently in cough mixtures than it is now.

The compound syrup of white pine of the National Formulary contains chloroform and morphin in addition to extracts of white pine, wild cherry, sanguinaria and other substances—a typical “shot-gun” mixture of nauseants, depressants of the respiratory center and stimulants of the bronchial mucous membrane.

26. The following incident illustrates the unfortunate results of interference in such cases. A patient suffering from a cough with free secretion received a mixture containing morphin, and expressed his satisfaction at the prompt relief afforded. Later he felt greatly discouraged because (as he supposed) he had “caught fresh cold,” which he attributed to his low resistance. In fact, the morphin suppressed the cough while the secretion continued, becoming purulent, and the necessary cough returned when the effects of the morphin had passed away.

Sore throat is best treated with gargles, sprays, or demulcents in the form of lozenges. A dilute solution of hydrogen peroxid is useful for cleansing the throat, or a hot 5 per cent. solution of potassium chlorate may be used as a gargle; to this may be added a few drops of solution of ferric chlorid. Small ulcers or areas of inflammation in the throat may be swabbed with cotton dipped in a mixture composed of one part of solution of ferric chlorid to ten parts of glycerin.

The official lozenges of ammonium chlorid are useful in treating sore throat but it is not easy to explain the effect of the ammonium chlorid in that case. Lozenges of elm bark allay slight irritation of the throat.

There are few conditions in which self-medication and its unfortunate consequences are more common than in coughs and "colds," and there is a striking similarity between the composition of nostrums advertised to physicians in numerous medical journals and that of the patent medicines, so-called, which are advertised directly to the public. It is obvious that it matters little, so far as the consequences are concerned, whether the patient dosés himself with Ayer's cherry pectoral or Jayne's expectorant, or has compound syrup of cocillana or glyco-heroin (Smith) prescribed for him by a physician.

DOSAGE

The nauseant dose of several of the emetics has been given. The dose of ammonium chlorid is commonly stated as from 0.3 to 1 gm. (5 to 15 grains) but it is much more frequently used in doses of 0.15 to 0.2 gm. (2 to 3 grains). The troches of ammonium chlorid each containing 0.1 gm. ($1\frac{1}{2}$ grains) with extract of glycyrrhiza, tragacanth and sugar, flavored with tolu, afford a convenient form of treatment for sore throat. It may be prescribed for cough (laryngitis or bronchitis) somewhat as follows:

	gm. or c.c.	
Ammonii chloridi	5	3 i
Syrupi acidi citrici	50	fl $\frac{3}{4}$ iss
Aquae	q. s. ad 100	fl $\frac{3}{4}$ iii

M. Sig.: One teaspoonful every two or three hours.

Ammonium chlorid has a disagreeable taste which is disguised somewhat by the acidity of the mixture.

Ammonium carbonate is given in doses of 0.25 gm. (4 grains). Physicians sometimes overlook the acid character of syrup of squill and prescribe it with the strongly alkaline ammonium carbonate.

A nauseant and sedative may be prescribed together somewhat as follows:

	gm. or c.c.	
Codeinae sulphatis	0 5	gr. viii
Syrupi ipecacuanhae	30 0	fl ℥ i
Aquae.....q. s. ad 100		fl ℥ iii

M. Sig.: One teaspoonful every two or three hours.

One should avoid the use of too much of the sedative in such cases, as this will lead to the total suppression of the cough. Terpin hydrate is given in doses of 0.12 gm. (2 grains) in powder, capsules or dissolved in elixir.

Many of the patent medicines, so-called, which are sold directly to the public, as well as those which are advertised directly to physicians, contain saponin derived from sanguinaria or other source, and a sedative such as heroin or morphin. No ready-made mixture is suitable for any considerable number of patients, because the doses of nauseants and sedatives should be adjusted carefully to the needs of each patient.

MATERIA MEDICA

Ammonii Chloridum. — Ammonium Chlorid, U. S. P., usually occurs as an odorless, white crystalline powder having a cooling saline taste. It is freely soluble (1:2) in water and soluble (1:50) in alcohol. Ammonium chlorid is incompatible with alkaline hydroxids and carbonates which liberate ammonia. In mixtures with the soluble salts of silver and of lead, the insoluble chlorids of these metals are formed.

Ammonii Carbonas. — Ammonium Carbonate, U. S. P.—The official ammonium carbonate consists of a mixture of acid ammonium carbonate and ammonium carbamate. It occurs as white hard masses, having a strong odor of ammonia and a sharp, saline taste. On exposure to air the salt loses both ammonia and carbon dioxid. It is slowly but freely soluble in water, the ammonium carbamate being thereby converted into normal ammonium carbonate. Alcohol dissolves the carbamate and leaves the acid carbonate.

Ammonium carbonate like other alkali carbonates is incompatible with acids and the soluble salts of most metals, and alkaloids. Among the preparations containing ammonium carbonate, the only one that is now at all widely used is:

Spiritus Ammonii Aromaticus.—Aromatic Spirit of Ammonia, U. S. P., a solution of ammonium carbonate with some free ammonia and aromatic oils in a mixture of water and alcohol. The actions and uses are the same as those of ammonium carbonate, the average dose being about 2 c.c. (30 minims).

Balsamum Tolutanum.—Balsam of Tolu, U. S. P., is a balsam obtained from *Toluiifera Balsamum*.

Syrupus Tolutanus.—Syrup of Tolu, U. S. P., is a saturated solution of the aromatic principles of balsam of Tolu in syrup.

Prunus Virginiana.—Wild Cherry, U. S. P., is the bark of *Prunus serotina*. It yields a small amount of hydrocyanic acid when moistened.

Syrupus Pruni Virginianae.—Syrup of Wild Cherry, U. S. P., is a syrup representing an aqueous extract of 15 w/v per cent. of wild cherry bark.

Terpini Hydras.—Terpin Hydrate, U. S. P., is the hydrate of the diatomic alcohol terpin. It occurs in colorless crystals, nearly inodorous, having a slightly aromatic but somewhat bitter taste. It is only slightly soluble in water (1:200) but much more soluble in alcohol (1:10), so that it may be administered in the form of an elixir, but this requires a rather large dose of alcohol.

CHAPTER X.—ARSENIC, ANTIMONY AND PHOSPHORUS

ARSENIC

Toxic doses of the strongly ionizable inorganic compounds of arsenic cause gastro-enteritis with vomiting, diarrhea and abdominal pain, these symptoms being commonly delayed for half an hour or more. The first symptom frequently is a feeling of constriction in the throat with difficulty in swallowing. The evacuations are normal in appearance at first but later become watery and contain shreds of desquamated intestinal epithelium closely resembling the "rice-water" stools of Asiatic cholera. The fluid, unlike that of simple diarrhea induced by saline cathartics, consists of the serum of the blood, or it may also contain some blood, and this loss of serum results in a train of symptoms closely resembling those of actual hemorrhage. There is weakness, dizziness, headache, cold sweat and collapse. The features are pale and shrunken, the pulse weak, the respiration deep, later depressed. The symptoms are intensified until coma and death occur. Convulsions may occur (asphyxial) or they may be absent. The urine is commonly diminished or totally suppressed, because of the increased viscosity of the blood and the lowered blood pressure. Death may result from either circulatory or respiratory failure, that is, either the heart or the respiration may fail first, but when both are affected so profoundly each reacts upon the other, so that one cannot say that either alone is the cause of death.

The gastro-intestinal symptoms have been attributed to the local irritant action of arsenic, but they are now considered as the effects following absorption, and are explained in the following way: Arsenic causes paralysis of the walls of the capillaries, and later those of the arterioles, especially of the splanchnic region, rendering them more permeable than normally, so that



there is a copious effusion of serum or even of blood, into the tissues. After the administration of very large doses of arsenic to animals one may observe extravasations of blood beneath large areas of the peritoneum. The escape of serous fluid raises blisters beneath the gastro-intestinal mucous membrane, and this is soon desquamated with the escape of large amounts of serum into the stomach and intestine, causing the "rice-water" diarrhea. The diarrhea and its attendant pain and loss of water cause a great fall in the blood pressure, and this is later augmented by the direct action of the arsenic on the heart, should the patient survive long enough for this action to take place.

Such serious disturbances of the circulation are always attended with corresponding depression of the central nervous system; especially is this true when the circulatory changes are induced suddenly. One has only to recall the frequency of dizziness due to interference with the cerebral circulation when one rises suddenly from a sitting or recumbent position, to appreciate that the great loss of serum in arsenic poisoning and the resulting circulatory disturbance must cause a variety of secondary effects.

If vomiting occurs early the symptoms may be of almost any degree of severity, because much, or comparatively little, of the arsenic may be evacuated thereby, dependent partly on the amount which has passed into the duodenum, or the poisoning may take on an extremely chronic character, even from a single dose.

There should be little difficulty in diagnosing chronic arsenic poisoning following the typical symptoms of acute poisoning, or where it is known that a large dose of arsenic has been taken, but the symptoms resulting from the repeated administration of very small amounts are often obscure and require patience for their recognition.

The symptoms of acute and chronic arsenic poisoning are discussed in greater or less detail in almost all text-books of pharmacology and materia medica, and every physician should familiarize himself with these

symptoms because of the frequency with which this type of poisoning occurs.

It will suffice for our purposes at present to enumerate some of the symptoms of the chronic type, merely to show the necessity for more careful study than it commonly receives. The symptoms are sometimes divided into three stages; in the first there is lassitude, loss of appetite, and there may be nausea and vomiting. This stage might lead one to suspect the presence of typhoid fever. The intestinal symptoms may be present, or they may be absent. In the second stage there may be symptoms resembling those of a "cold" owing to the irritation of the mucous membranes of the larynx and nose and of the conjunctiva. Various affections of the skin are described as occurring in this stage, including a typical discoloration or blackening.

In the third stage there are disturbances of sensation and motion in the hands and feet, and peripheral neuritis, together with numerous other manifestations which require careful consideration. The symptoms are not sharply marked off in the stages mentioned, but many of those commonly described as belonging to the second or third may appear earlier than this classification would indicate.

When vague symptoms lead one to suspect even the possibility of chronic arsenic poisoning the urine should be examined for traces of the metal. Of course one would not expect to obtain evidences of the poison by the grosser tests, but, on the other hand, the most delicate tests enable one to detect the faintest traces of arsenic in the urine. Such traces have comparatively little significance unless this evidence is supported by others of great weight, because traces of arsenic may be derived from foods containing it, either as a natural or as an added ingredient.

Chronic arsenic poisoning is attended with degenerative changes in the walls of the capillaries and later in the intestinal epithelium, and in various organs, including the heart, liver and kidneys.

Icterus results from the changes in the liver, and effusions occur in various tissues, that into the eyelids

being usually early and fairly characteristic. The damage to the heart may fail to attract attention in the presence of other symptoms, such as nephritis, to which the attention may be mainly directed if the true cause of the trouble is not suspected.

The toxicology of arsenic is interesting from various standpoints. It played an important rôle in the crimes of professional poisoners in earlier times, and it is still employed occasionally for purposes of murder and suicide. It lends itself, unfortunately, to the poisoning of one member of a household by another when small doses can be administered frequently, because, owing to its tastelessness and lack of odor, it does not arouse suspicion and is all too easily obtained in the form of rat poison. All arsenic preparations which might be used in this way should be colored distinctively by the addition of lamp-black or indigo which cannot be mixed with most foods without attracting attention.

Fortunately, the metal can be detected in the vomitus, urine and feces, and in the cadaver long after death, so that it is probable that few adults die of acute arsenic poisoning without the fact becoming known.

The treatment of acute arsenic poisoning requires further investigation. It was accepted for many years as an established fact that as soon as possible after a poisonous dose of arsenic had been swallowed the patient should receive a large dose of moist ferric hydroxid, or preferably, the hydroxid with magnesia, which can be prepared more conveniently and quickly, when the materials are at hand.

Serious doubt has been thrown on the value of this procedure during the past few years, and the stomach should be washed out as promptly as possible whether the iron antidote be employed or not. Active catharsis should be induced with magnesium sulphate solution in order to remove any of the poison that has passed into the duodenum. Since prompt purgation is necessary in such cases, a large dose of the dilute solution of magnesium sulphate should be administered—preferably a pint of solution containing about an ounce of the salt. Naturally, purgatives are contraindicated after the intestinal symptoms have developed.

The elimination of arsenic depends somewhat on the way in which it is administered. When a toxic dose has been taken by the mouth the larger part may be evacuated with the vomitus, or with the washings of the stomach, and a large part of the remainder may be evacuated in the feces, especially if prompt purgation is induced. After absorption into the circulation arsenic may be found in almost all the body tissues. Elimination goes on very slowly indeed, so that months may elapse before it ceases to appear in the secretions, and some of it appears to be retained almost indefinitely.

A larger portion of the poison is said to be eliminated by the intestine after its oral administration, and a smaller part in the urine, but after the subcutaneous injection the kidneys eliminate more than the gastrointestinal tract. Diuretics should be administered after the subcutaneous injection of a poisonous dose if the patient is seen early, but caffeine and theobromin will have little or no effect after the appearance of the "rice-water" stools because of circulatory disturbances previously mentioned; hence it would seem probable that the intravenous injection of a 2 per cent. solution of sodium sulphate, as mentioned in connection with strychnin poisoning, might be of benefit, but we are unaware of any experiments bearing on the subject.

The extraordinarily slow elimination of arsenic and its consequent tendency to accumulate in the body and to produce chronic poisoning are of especial interest in connection with the uses of arsenic in fabrics, and food preservatives.

A manufacturer of a food product used anilin to color it, the finished food as eaten containing about one part of arsenic in 20,000 million parts of food. He was probably unaware of the presence of arsenic in the anilin, and it would require about 1,000 tons of the food to furnish an amount of arsenic equal to a toxic dose for a man; nevertheless it was maintained that the practice was unlawful, though it could hardly be held that enough arsenic could be taken in that way to produce any perceptible effect in a life time, especially, as arsenic is frequently taken over long periods for its

medicinal effect. Quite a different case was that of a manufacturer whose candy was found to contain six parts of arsenic per million. One pound of the candy contained as much as an average dose of arsenic for an adult, and its continued use in large amounts might very well cause symptoms.

In seeming contradiction to the preceding statement is the well-known fact that the administration of small and increasing doses of arsenic by the mouth leads to a higher degree of tolerance, apparently through an acquired resistance to absorption from the gastrointestinal tract, for such tolerant animals are not more resistant than others to arsenic administered subcutaneously. Remarkable stories of tolerance are commonly told of the arsenic eaters of Tyrol.

As little as 0.1 gm. ($1\frac{1}{2}$ grains) of arsenic has proved fatal, but very much larger oral doses have been survived, and if vomiting occurs within less than half an hour after a fairly large dose has been swallowed the chances of recovery are fairly good, but of course one cannot depend on this alone, and other treatment should be instituted, as previously stated. There is an unfortunately widespread belief among the laity that larger doses of arsenic may be safer than smaller, but toxic, ones.* This is doubtless based on the fact that large doses do occasionally induce emesis in time to save life, while smaller doses may prove fatal.

In view of what has been said of the widespread use of arsenic in the arts, in medicine and in foods, with the consequent frequency with which at least small amounts may be taken without the knowledge of the patient, and the extreme slowness with which elimination takes place, it is obvious that the detection of traces of arsenic in the excreta or in a cadaver does not prove that observed symptoms or death resulted from arsenic in a given case, and one will understand the necessity of a careful study of the actions of arsenic before expressing opinions that may be of far-reaching importance.

The administration of small amounts of arsenic to young animals may cause them to grow more rapidly

than other members of the same litter that receive the same food without the arsenic. Several observers found that the bones of the animals that received arsenic were longer and thicker than those of the controls; that their fur was glossier, and other evidences of rapid development were also observed, but these effects are not always obtained and other investigators came to different conclusions with regard to the effects of arsenic on metabolism. Poisonous doses cause fatty degeneration in various organs, and other disturbances of metabolism.

Various explanations have been offered to account for the more rapid growth observed as the result of the use of arsenic, but it seems possible that the actions on the capillaries and the effects on the general circulation together with the stimulation of production of red blood corpuscles or of hemoglobin are concerned in the effects on metabolism.

It also seems possible that arsenic may serve to correct some adverse conditions entailed in those feeding experiments in which the greater growth was observed, for it does not seem probable that arsenic would influence growth favorably if the animals were kept under the best conditions of living and exercising in the open air. At least, no one would think of advising the routine administration of arsenic to healthy little children living under hygienic conditions.

Certain of the organic compounds of arsenic which ionize but little are much less active than the inorganic compounds that have been discussed. Cacodylic acid, which differs from arsenic acid by having two methyl groups in place of two hydroxyls of the latter, has long been known, the sodium salt having been introduced about fifty years ago. Sodium arsanilate was introduced into therapeutics in 1902 under the name of atoxyl under the mistaken impression that it was non-toxic. It exerts the arsenic action, though less violently than arsenic trioxid in equal weights, and in addition it is prone to cause blindness through atrophy of the optic nerve. When atoxyl was submitted to the Council on Pharmacy and Chemistry its composition was investigated, and it was shown that the arsenic is not

present in the trivalent state as had been supposed, but in the pentavalent.

Following the introduction of organic compounds of arsenic, Ehrlich investigated a large number with the object of finding one capable of exerting the well-known trypanocidal action of the metal without the toxic action on the host, or at least of finding a compound in which the relative toxicity for the parasite and the host would permit of the administration of a single dose that would at once destroy all the micro-organisms in the blood.

As a result of this search Ehrlich and his co-workers brought out salvarsan, or arseno-benzol, more correctly called arsen-phenol-amine hydrochlorid. It has also been named "606" in reference to the laboratory number given the compound.

From the results of the early studies it was announced that a single dose of salvarsan was capable of destroying all of the micro-organisms of syphilis in the human body in suitable cases. It was also highly extolled in the treatment of various other diseases, including relapsing fever, and at the same time it was said to be relatively harmless to man in the dosage advised.

The literature relating to salvarsan is already enormous, and while it is not feasible to review this even partially, it may be said that a single dose apparently effects a complete cure only when it is given shortly after infection, if at all, and that it is far from being harmless, numerous deaths being undoubtedly attributable to its use even with the most careful technic.

Unfortunately, the spirochetes of syphilis may become more resistant than normal to arsenic after repeated doses, and it is usually necessary to combine the use of arsenic with that of mercury.

Neosalvarsan is a soluble compound of salvarsan thought by some to be tolerated better than the original product.

THERAPEUTIC USES

Arsenic trioxid is applied to ulcerated surfaces as an irritant, but its use is attended with severe pain. It has long been used in domestic practice and occa-

sionally by physicians as a caustic for the removal of malignant growths, in the form of pastes. The action cannot be controlled accurately, it is very painful and there is some danger of the absorption of a poisonous dose when it is applied in this way. Its use is not recommended. It has long been employed and is still used as an application to ulcerated surfaces and by dentists for destroying the nerves in carious teeth.

It is used internally in a variety of disorders in which its mode of action cannot be explained satisfactorily. For example, it is used in neuralgia of a periodic character, and in chorea, in which it is of doubtful value. It is used in anemia, in which it probably stimulates the organs involved (bone marrow) to a more rapid regeneration of the red blood corpuscles or the hemoglobin. It is also used in pernicious anemia, in leukemia and in Hodgkin's disease (malignant lymphoma, or hypertrophic disease of the lymphatic glands of the body, attended with anemia). In these diseases its temporary effects are often markedly beneficial, but relapses almost invariably occur.

It is often used to improve the nutrition when the disturbance results from obscure causes, but, of course, it is not suited for use in all of those cases.

It has been recommended for use in diabetes, but like other drugs, it usually fails in that condition.

Arsenic is said to be useful in various skin diseases, such as psoriasis, lichen planus, chronic eczema, pemphigus, dermatitis herpetiformis, chronic urticaria and disturbances involving the sweat glands. It must be remembered, however, that the treatment of skin diseases by the general practitioner involves many difficulties because of the obscurity of the etiology in these conditions, hence they should be referred to a dermatologist when they present unusual difficulties or conditions with which the practitioner is unfamiliar.

Attention has been called to the fact that the fur of animals used in experiments with arsenic was glossier than that of the controls, and horse dealers have long utilized this action of arsenic in improving the coats of horses. These results suggest the use of arsenic in man when there is faulty nutrition of the skin.

Acute inflammation of the skin contraindicates the use of arsenic.

The organic compounds of arsenic have a distinct field of usefulness in various diseases of protozoal origin, including sleeping sickness (trypanosomiasis), malaria, relapsing fever and syphilis, but the side actions, especially that on the optic nerve (with atoxyl), have greatly interfered with its use. Sodium arsanilate (atoxyl) was used extensively for a time in the treatment of sleeping sickness; but numerous cases of blindness resulted, and it has fallen into disuse for that purpose.

Arsenic has long been used in malaria, especially in the chronic forms which have resisted quinin, arsenic and quinin being commonly used together in those cases.

The cacodylate attained to some degree of importance many years ago when it was found that it exerts the actions of arsenic over a longer period than the inorganic forms and that it is less toxic.

Salvarsan is widely used in the treatment of syphilis; it is given alone soon after infection or in combination with mercury in the later stages. It is also employed in the treatment of relapsing fever and in many other conditions, sometimes with good results, sometimes with harmful effects.

The results reported soon after the introduction of salvarsan raised hopes which subsequent experience proved were far too optimistic, but when the early literature has been discounted sufficiently we still have in it a valuable remedy.

Headache, nausea and malaise commonly follow the intravenous injection of salvarsan, the symptoms lasting from twelve to twenty-four hours. Aside from these after-effects certain nervous effects have been observed. These symptoms — termed nervous relapse — are believed to be due to an increased activity of the spirochetes and they call for another dose of salvarsan or treatment with mercury.

Arsenic is sometimes used in the most diverse conditions including asthma, tuberculosis, bronchitis, leu-

kemia, splenic anemia, and in numerous other diseases, and one is led to suspect that when improvement follows its use in those conditions it is merely a coincidence or that this improvement is attributable to the effects of arsenic on metabolism in general rather than to any direct effect on the diseased organs or the causes of the disease.

All forms of arsenic should be used cautiously or not at all in the presence of disease of the eye, especially of the retina, even if it be of syphilitic origin, because of its tendency to induce optic neuritis and blindness, but salvarsan is said to cause optic neuritis in few instances. Arsenic is contraindicated in severe cardiac and renal disease, and salvarsan should be used cautiously in syphilitic infants because of the danger from liberated endotoxins when the spirochetes are destroyed.

DOSAGE

For ordinary affections of metabolism or for a tonic influence arsenic trioxid is given in doses of from 0.001 to 0.002 gm. ($\frac{1}{60}$ to $\frac{1}{30}$ grain). In syphilis the dosage should be regulated according to the effect induced, but it is well to use as large doses as the patient will tolerate.

The various forms of inorganic arsenic are frequently administered in increasing doses until symptoms of mild intoxication appear. One may begin with 0.003 gm. ($\frac{1}{20}$ grain) of arsenic trioxid, three times a day, and increase by 0.001 gm. ($\frac{1}{60}$ grain) three times a day: that is, 0.004 gm. ($\frac{1}{15}$ grain) three times on the second day, 0.005 gm. ($\frac{1}{12}$ grain) three times on the third, etc., until symptoms of arsenical intoxication are induced.

Solution of potassium arsenite and solution of arsenous acid may be given in doses of 0.2 c.c. (3 minims) three times a day, and increased by 0.05 c.c. (1 minim) three times a day. A slight toxic effect is indicated by nausea, colicky pains or a puffiness under the eyes. The presence of albumin in the urine may also be observed. Such symptoms may make it advisable to discontinue the administration of the drug for a time.

Solution of arsenous and mercuric iodids is usually administered in doses of 0.1 c.c. ($1\frac{1}{2}$ minims).

Sodium arsenate is given in doses of 0.003 to 0.005 gm. ($\frac{1}{20}$ to $\frac{1}{10}$ grain) three times a day and increased as with other preparations of arsenic.

Of the organic combinations of arsenic, sodium arsanilate, (atoxyl, soamin), is given in doses of 0.02 gm. ($\frac{1}{3}$ grain) gradually increased, and sodium cacodylate may be given in doses of 0.03 gm. ($\frac{1}{2}$ grain). Sodium arsanilate is used only by injection; the cacodylate is frequently administered hypodermically though it may also be administered by mouth.

The dose of salvarsan is 0.5 gm. ($7\frac{1}{2}$ grains). Since it is not suited for oral administration it must be given intravenously, subcutaneously or intramuscularly, but intramuscular injections have been followed in several instances by the toxic effects of arsenic; furthermore, the intramuscular injection is painful and is usually followed by a painful inflammatory nodule which persists for some time. It is seldom employed intramuscularly by those who have mastered the technic of the intravenous injection, and no one should undertake to administer salvarsan intravenously without having mastered the somewhat difficult technic.

Salvarsan, being acid, is neutralized and suspended in a neutral fluid for subcutaneous or intramuscular injection. A clear solution in sterile alkaline fluid is used for intravenous injection.

The powder decomposes rapidly on exposure to the air, and suspensions and fluids intended for injection should be used at once. If any part of the contents of a tube remains unused when a dose is administered it should under no circumstances be mixed with a subsequent dose but should be thrown away. Even those tubes that are cracked before being used, permitting the action of the air, should be rejected. The water used for making intravenous injections should be distilled shortly before being used. Various forms of apparatus are advised by different authorities, but most of the apparatus employed for the injection can be had in any first class pharmacy or instrument maker's shop.

MATERIA MEDICA

Arseni Trioxidum.—Arsenic Trioxid, U. S. P., formerly official as arsenous acid, also called arsenic trioxid or arsenious anhydrid, As_2O_3 , occurs as a white powder or in irregular masses of two varieties, one amorphous, transparent and colorless like glass, the other crystalline, opaque and white resembling porcelain. Arsenic trioxid is very slowly soluble (glassy variety 1:30, porcelain variety 1:100) in water and practically insoluble in alcohol. It dissolves quite readily in solutions of acids or alkalis, in which form it is very widely employed in preference to pills or tablets of arsenic trioxid itself.

Liquor Potassii Arsenitis.—Solution of Potassium Arsenite, U. S. P., commonly known as Fowler's solution, is an aqueous solution containing potassium arsenite, corresponding to 1 per cent. of arsenic trioxid. The preparation has a distinctive color and odor from the addition of 3 per cent. of compound tincture of lavender. The solution is frequently somewhat alkaline and is therefore incompatible with alkaloidal salts.

Liquor Acidi Arsenosi.—Solution of Arsenous Acid, U. S. P., is an aqueous solution containing the equivalent of 1 per cent. of arsenic trioxid with 5 per cent. of hydrochloric acid. It occurs as a clear, colorless, odorless liquid, having an acidulous taste and an acid reaction.

Liquor Arseni et Hydrargyri Iodidi.—Solution of Arsenous and Mercuric Iodids, U. S. P., commonly known as Donovan's solution, represents, 1 per cent. of arsenous iodid and 1 per cent. of mercuric iodid. It occurs as a clear, colorless, or pale yellowish, odorless liquid, having a disagreeable metallic taste.

Sodii Arsenas.—Sodium Arsenate, U. S. P., the sodium salt of arsenic acid, occurs as colorless transparent monoclinic prisms, odorless and having a mild alkaline taste. It is freely soluble (1:12) in water but nearly insoluble in alcohol.

Sodium Arsanilas.—Sodium Arsanilate, N. N. R., also known as sodium anilin arsonate, sodium aminophenyl arsonate and sodium aminarsonate, is more

widely known by one or the other of its trade names; atoxyl, which is marketed with 3 molecules of water, and soamin, which occurs in trade with 5 molecules of water. Sodium arsanilate, the sodium salt of arsanilic acid, occurs as white, odorless crystals, having a faintly saline taste and being freely soluble (1:6) in water and only slightly soluble (1:125) in alcohol. When the aqueous solution is allowed to stand it assumes a yellowish tint. Sodium arsanilate is incompatible with acids, alkalies and salts of mercury. It is readily decomposed in the stomach and is now administered only by injection, preferably in simple solution.

Sodii Cacodylas.—Sodium Cacodylate, N. N. R., is also known as sodium dimethylarsenate, and is the sodium salt of dimethyl arsenic acid. It occurs as a white powder, very soluble (1:0.5) in water and freely soluble (1:1) in alcohol. The aqueous solution is alkaline toward litmus paper, but nearly neutral toward phenolphthalein. It is comparatively stable and may be given either in solution or in the form of pills or tablets.

Salvarsan.—Salvarsan, N. N. R., also known as arsenobenzol, "606," and arsenphenolamin hydrochlorid, is 3-diamino-4-dihydroxy-l-arseno-benzene hydrochlorid. It contains 31.57 per cent. arsenic. It occurs as a yellowish crystalline hygroscopic powder, very unstable in air. It is soluble in water, yielding a solution with an acid reaction. It is marketed only in glass tubes and, as noted above, care should be exercised to see that these tubes are intact and that the powder has not been exposed to air.

Neosalvarsan is the name applied to a mixture of sodium 3-diamino-4-dihydroxy-l-arsenobenzene-methanal-sulphoxylate with inert, inorganic salts. The arsenic content of 3 parts of neosalvarsan is approximately equal to 2 parts of salvarsan. Solutions of neosalvarsan are more readily prepared than those of salvarsan. Its actions and uses are the same as those of salvarsan, and the same precautions are to be observed when it is employed.

ANTIMONY

The systemic effects of antimony resemble those of arsenic so closely that they do not require detailed discussion, but it is important to remember that the early vomiting and diarrhea following the use of toxic doses of antimony may be due to local action, though early vomiting usually serves to prevent the occurrence of severe toxic symptoms.

The occurrence of diarrhea, on the other hand, indicates that the poison has either entered the duodenum or has been absorbed, and both may occur. Should the administration of the usual emetic dose of antimony fail to produce vomiting, as sometimes happens, poisoning may result unless the drug is removed from the gastro-intestinal tract. When there is reason to fear its toxic action efforts should be directed toward its removal, as in the case of arsenic.

Limewater, a pint or less, the oxid or carbonate of magnesia, or tannin should be administered,²⁷ and the stomach washed promptly and thoroughly. If precipitants are not at hand no time should be lost in efforts to get them before washing the stomach. After the stomach has been washed the patient should receive 30 gm. (1 ounce) of magnesium sulphate in about 500 c.c. (1 pint) of water in order to remove any of the antimony that has passed into the intestine.

If antimony remains in the gastro-intestinal tract for a sufficient length of time corrosion occurs, with absorption, and the gastro-intestinal symptoms are augmented by the systemic actions of the poison in the way described under arsenic, and in that case washing of the stomach and saline purgatives would be of little use, though they would at least do little harm.

Antimony is usually absorbed very slowly indeed, hence its longer sojourn in the gastro-intestinal tract favors the local irritant action, and interferes correspondingly with its use for the systemic effects.

This slow absorption with the resulting prolonged local gastro-intestinal action is the basis for its use as

27. Cushny advises the use of strong tea as a precipitant for antimonial salts.

a nauseant, otherwise it would be inadmissible to employ so toxic an agent for that purpose while we have so many harmless agents that are capable of inducing nausea.

As little as 0.15 gm. $2\frac{1}{2}$ grains) has caused death when vomiting was delayed or absent, but such an occurrence is rare, and much larger doses have been survived.

Severe poisoning seldom follows the therapeutic use of antimony at present, because it is little used except as a nauseant, the dose for this purpose being too small to cause toxic symptoms even though absorption takes place, and emesis nearly always occurs if large doses are employed.

Numerous investigators have sought to utilize compounds of antimony in the treatment of trypanosomiasis and syphilis, following the observation that tartar emetic is rapidly destructive to trypanosomes in mice.

A single intramuscular injection of a suspension of an insoluble salt of trivalent antimony, or of the metal itself, destroys the trypanosomes in mice, but the latter die of chronic antimony poisoning.

Antimonous oxid (Sb_2O_3), containing trivalent antimony, is destructive to trypanosomes, and may be administered intramuscularly in the form of a 30 per cent. oily suspension. Ointments containing insoluble compounds of antimony have been used successfully in the treatment of experimental trypanosomiasis.

Compounds containing pentavalent antimony are much less active than those containing the trivalent.

But for the difficulty of securing the systemic action without the gastro-intestinal disturbances, antimony might be used for almost any of the purposes for which arsenic is employed. It is still used in psoriasis when the condition fails to yield to other forms of treatment, and it is used occasionally for trypanosomiasis.

The systemic effects are best attained by intravenous injection, the subcutaneous injection being too painful.

DOSAGE

Certain of the uses and doses of antimony have been discussed under the emetics. Camac states that he used from 0.01 to 0.015 gm. ($\frac{1}{6}$ to $\frac{1}{4}$ grain) of the sodiotartrate about once a week, in the treatment of a case of sleeping sickness which had apparently become resistant to atoxyl.

The ointment was formerly used externally but it sometimes produced extensive abscesses and is now rarely employed.

For materia medica see Emetics.

PHOSPHORUS

The action of phosphorus resembles that of arsenic and antimony to a certain extent. Thus the administration of very small amounts to young animals causes an increase in the growth of bones, apparently through stimulation of the osteoblasts. At the same time it causes the deposit of dense bone in cancellous tissue, but the prolonged administration causes the absorption of the latter. Small doses of phosphorus have much less effect on the bones of adult animals, but these also show some deposit of dense bone.

Phosphorus, like arsenic, causes some increase in the red blood cells, though it does not appear to increase the total amount of hemoglobin in the blood. Small doses do not appear to induce other notable pharmacologic actions unless long continued.

There are usually no symptoms observed immediately after a poisonous dose of phosphorus has been taken by the mouth, but after some hours there is gastro-intestinal pain with vomiting and sometimes diarrhea. The vomited matter has a garlic-like odor, and this with the phosphorescence which it exhibits in the dark, are characteristic and suffice for a diagnosis in otherwise doubtful cases.

Following the early symptoms there is usually a period of several days during which the patient suffers no disturbance, after which he may be seized again with vomiting and diarrhea; the liver is enlarged and tender; the patient is jaundiced and suffers prostration with its attendant circulatory disturbances, partly

due to the direct action of the poison on the heart. Hemorrhages occur in various tissues, and the vomitus, feces and urine may contain blood.

There is a fatty infiltration of the liver, heart and other organs, secondary to the disturbances of metabolism, whereby there is an increased destruction of protein. Death from heart failure occurs in about one week in fatal cases, but severe symptoms may be followed by recovery, in which case the organs that have been infiltrated with fat become cirrhotic from the proliferation of interstitial connective tissue; but it is said that this occurs more markedly in poisoning by repeated doses than after a single large dose. This cirrhosis affects the liver and gastro-intestinal tract to a greater extent than the kidneys, and these effects of course induce the usual secondary results.

Acute phosphorus poisoning sometimes occurs from swallowing rat paste. It is very slowly absorbed from the gastro-intestinal tract, and when the patient is seen shortly after the poison has been swallowed the efforts should be directed toward removing as much of it as possible and oxidizing the remainder. The stomach should be washed with a very dilute solution of copper sulphate, 2 gm. (30 grains) in about 500 c.c. (1 pint) of water, or 2 gm. (30 grains) of copper sulphate dissolved in 50 c.c. (2 fluidounces) of water may be administered as an emetic, and about 0.1 gm. ($1\frac{1}{2}$ grains) may then be administered in a glass of water with a view to causing the phosphorus remaining in the stomach to become coated with metallic copper; this being rapidly converted into an insoluble phosphid. As an alternative to the use of copper sulphate in the wash water, and later, one may wash the stomach with a large amount of solution of potassium permanganate, 0.1 to 0.2 per cent., and later administer a glassful of water containing 0.3 gm. (5 grains) of potassium permanganate. As this salt attacks organic matter and other readily oxidizable substances, it is much more effective in oxidizing poisons if it be given after the stomach has been washed than if it be given while the stomach is filled with food.

Hydrogen peroxid and oil of turpentine are sometimes recommended as oxidizing agents in phosphorus poisoning, but the peroxid is decomposed so rapidly in contact with mucous membranes and body fluids that it can act on the phosphorus only if it be brought into immediate contact with it in the stomach, and oil of turpentine is also of doubtful value.

Unless the stomach is emptied almost immediately after the phosphorus has been swallowed, some of it will have passed into the duodenum, where it will be out of reach of the antidotal measures just discussed; it is absorbed very slowly indeed, and the intestine should be emptied as promptly as possible, preferably by using a large dose of magnesium sulphate, 30 gm. (1 ounce) dissolved in about 500 c.c. (1 pint) of water. A small dose of copper sulphate may be dissolved in the solution of magnesium sulphate if it be at hand, or it may be administered later.

Fats and oils should be avoided while the phosphorus remains in the gastro-intestinal tract, as they interfere with the efforts at oxidation and favor absorption of the poison.

When later symptoms of phosphorus poisoning have developed alkalies should be given, preferably citrates and bicarbonates, to neutralize the large amount of acid formed in the tissues.

Workmen employed in factories where white or yellow phosphorus is used are subject to a peculiar necrosis of the jaw bone which was formerly attributed to the action of phosphorus that had gained access through carious teeth; but it seems probable that the bone is first affected by phosphorus that reaches it through the circulation, rendering it susceptible to bacterial action. This truly terrible affliction is less common when red "amorphous" phosphorus is used, and is almost unknown when the sesquisulphid of phosphorus is employed, as it now is quite commonly in the manufacture of matches.

THERAPEUTIC USES

Phosphorus favors the deposition of calcium in growing bones, and it is probably useful in osteomalacia, in rickets and possibly in bone that is undergoing

repair; but the action on the blood corpuscle formation does not justify its use in anemia, in which iron and arsenic are preferable.

It has been used in various affections of the central nervous system for its supposedly tonic or stimulant action, but it has little direct action on the central nervous system, and there is no evidence of its value in these conditions for which it is recommended principally by the manufacturers of nostrums intended to supply phosphorus in a form more readily available than that in the inorganic phosphates, and it is used less by educated physicians for such purposes than formerly.

The difficulties involved in the therapeutic use of phosphorus in the elemental state have led to the introduction of various compounds intended to supply phosphorus to the organism, and while it is possible that some of these preparations may have therapeutic properties, their advantages are not very obvious; but, on the other hand, there is no question that rational therapeutics has been interfered with by the sensational way in which most of them have been advertised.

Among the first of these compounds were the hypophosphites, which were introduced into therapeutics about half a century ago by Churchill, who supposed that they influenced nutrition favorably and who therefore advised their use in tuberculosis.

It has long been stated that the hypophosphites undergo little or no change in the body and that they are excreted in the urine practically unchanged. Nevertheless they continue to be exploited widely in the form of various nostrums.

One of the most widely advertised — hence one of the most popular — of these is Fellows' syrup of the hypophosphites. It contains several bases, in combination with hypophosphorus acid, quinin and strychnin, to which is probably due any medicinal value that the preparation may have. It is unnecessary to prescribe an expensive nostrum of this type merely because one wishes to give his patient small doses of quinin or strychnin. The official compound syrup of the hypophosphites is little better than the nostrum just men-

tioned, and contains nine supposedly medicinal ingredients in syrup. It is not in keeping with modern therapeutic teaching to use such complex mixtures.

The continued influence of Churchill's teaching is also evident in the formulas of many of the proprietary emulsions of cod-liver oil that are advertised to physicians and to the public. Nearly all of them contain mixtures of hypophosphites that can serve no useful purpose, but usually render the preparation more disagreeable to the taste.

When it began to be accepted by educated physicians that the hypophosphites were superfluous, other phosphorus compounds were introduced and glycerophosphates, lecithin and nuclein were offered.

Lecithin is abundant in various tissues and is especially abundant in eggs, but it is sometimes claimed that the raw or combined forms of lecithin, such as that existing in eggs, cannot be utilized so well as the uncombined. It is obvious, however, that the healthy organism is capable of obtaining its normal supply from the lecithin-bearing compounds of the food, and there is no evidence that the free substance is ever necessary. The average diet of a healthy man contains from 5 to 15 gm. (75 to 225 grains) of lecithin, and this can be increased easily when patients can take an abundance of egg-yolk.

Glycerophosphoric acid consists of phosphoric acid in which an atom of hydrogen has been replaced by the glycerin radical, and has the formula $H_2(C_3H_5(OH)_2)PO_4$. The glycerophosphates of calcium and of sodium are described in New and Nonofficial Remedies.

Lecithin consists of the ester of oleic, stearic, palmitic or other fatty acid with glycerophosphoric acid combined with cholin; hence it is spoken of as a phosphorized fat. The lecithins obtained from different sources differ somewhat in their composition, but this does not appear to be of any great importance in regard to their utilization by the body.

The nucleins consist of proteins combined with nucleic acid and are derived from the nucleoproteins of cells. Nucleic acid varies slightly but not essentially,

in its composition, depending on the source from which it is obtained, that from yeast cells — the usual source of commercial nucleins and nucleic acid — containing almost exactly 10 per cent. of phosphorus.

The composition of the nucleins varies rather widely with the method of preparation, but nucleic acids are definite chemical substances. They may be decomposed, yielding phosphoric acid, a carbohydrate, and purin and other bases.

Liver, kidney, brain and sweetbread are rich in nucleoproteins, hence in nucleic acids, and these foods may be used when it is desired to administer nuclein or nucleic acid, but lean meats are relatively poor in nucleoproteins. The purin bases derived from nucleoproteins are the precursors of uric acid; hence brain, liver, kidney, and sweetbread are to be withheld when the formation of uric acid should be limited as much as possible.

Lecithin, the glycerophosphates, nuclein and nucleic acid are discussed in New and Nonofficial Remedies.

Sanatogen is one of the many compounds that are exploited as containing a particularly active form of phosphorus. This product has been referred to on several occasions in the reading pages of THE JOURNAL and is discussed at some length in "Nostrums and Quackery."

DOSAGE

The average dose of phosphorus is 0.5 mg. ($\frac{1}{120}$ grain), to be given several times daily. A somewhat larger daily dose is recommended in osteomalacia, in which as much as 5 mg. ($\frac{1}{12}$ grain) may be given in the course of a day; but such doses cannot be considered altogether safe.

Phosphorus may be given in pills which may be made by using one of the many fairly permanent mixtures of phosphorus with suet, wax, or rosin, or by triturating phosphorus with a little sulphur under water, until liquefied; the water is poured off and a suitable excipient added. It may also be given dissolved in olive oil or cod-liver oil, or in alcoholic solu-

tion in the form of an elixir. It may be prescribed for children somewhat as follows:

Phosphorus	0.01 gm.	$\frac{1}{8}$ grain
Cod-liver oil....to make	100 gm.	3 fluidounces

Free the oil of contained air by heating to 150 C. and allow to cool, then add the phosphorus and warm to about 80 C. and shake until the phosphorus is entirely dissolved.

Two teaspoonfuls of this solution may be given daily, but it is said that even this amount taken daily for several days has caused death, and its use is not recommended.

For alcoholic solutions, the phosphorus is preferably dissolved in chloroform and mixed first with absolute alcohol, then with a mixture of alcohol or glycerin and elixir, care being taken to keep well within the solubility of phosphorus in the several solvents.

Practically all of the preparations of phosphorus deteriorate on keeping and, if it is desired to give this substance in an active form, care must be exercised to have the mixtures freshly prepared from materials that will comply with the official requirements. It will also be necessary to see that proper precautions are observed to free the solvent, particularly an oil, a fat or a resin, of air or free oxygen so as to avoid deterioration as much as possible.

MATERIA MEDICA

Phosphorus, U. S. P., occurs in commerce as a semitransparent, wax-like solid, usually in the form of cylindrical sticks. It has a distinct and disagreeable odor and taste, is luminous in the dark when exposed to air and should be kept under water in well-closed vessels, in a moderately cool place, protected from light. Phosphorus is nearly insoluble in water, slightly soluble (1:350) in absolute alcohol or (1:400) in glycerin, and soluble (1:80) in fatty oils and in ether; also (1:25) in chloroform and very soluble (1:0.5) in carbon disulphid.

The official or medicinally active form of phosphorus may be converted by means of heat into the red or allotropic modification of the element. This red or

"amorphous" phosphorus is permanent in dry air, is insoluble in ordinary solvents, and is generally considered to be non-poisonous.

Calcii Hypophosphis. — Calcium Hypophosphite, U. S. P., which occurs as colorless, transparent crystals, small lustrous scales, or white crystalline powder, odorless and having a nauseating bitter taste. It is freely soluble (1:65) in water and is practically insoluble in alcohol.

Calcium hypophosphite is incompatible with iodids and oxidizing agents. Caution should be observed in dispensing the substance, as an explosion may occur when it is triturated or heated with substances rich in oxygen, particularly nitrates and chlorates, that may be affected by a powerful reducing agent. It is not recommended for therapeutic use.

CHAPTER XI.—THE HEAVY METALS AND THEIR SALTS

The salts of the heavy metals act locally as astringents, irritants or corrosives, dependent on the nature of the compounds which they form with the tissues; thus the lead salts, which are astringent when used in dilute solution, are corrosive when concentrated solutions are employed.

The intestinal mucous membrane acquires a certain degree of tolerance toward irritant action of the metals if small doses are given at first, and gradually increasing amounts are employed. The large amounts of arsenic taken by the arsenic eaters of Tyrol afford a well-known example of this acquired tolerance.

The salts of metals which dissociate readily into their ions have many actions in common after the absorption of toxic doses into the circulation. The marked differences in the effects commonly observed after their administration are attributable in part to differences in their rates of absorption, in part to differences in their rates of dissociation. Arsenious acid is absorbed fairly well from the gastro-intestinal tract and it dissociates readily, hence it is actively poisonous, whereas most of the salts of iron and lead are absorbed so slowly that toxic symptoms rarely follow the administration of single doses of them.

When soluble salts of the metals are administered they are partially converted in the duodenum into insoluble carbonates or into albuminates, in which form they may be absorbed, or they may pass into the large intestine, being converted into sulphids. A larger part of the dose of the metallic salts escapes absorption and the sulphid renders the feces black.

Slow as the absorption of the metals usually is their excretion is commonly even slower, so that they may accumulate in the body and give rise to symptoms of poisoning. This action is prominent in the case of lead, even when minute amounts are taken over prolonged periods.

Most of the metals are excreted through the large intestine mainly, and to a slight extent through the kidneys. The irritant action at the seat of elimination in the intestine may give rise to enteritis and diarrhea, aside from any local irritant action and diarrhea induced by the unabsorbed portion, as with calomel.

The excretion of metals by the kidneys may give rise to nephritis, this being especially prominent after poisoning with mercuric salts.

The intravenous injection of toxic doses of the metallic salts or the rapid absorption of one of the arsenites, such as potassium arsenite, causes a rapid fall of blood pressure due to the direct action on the heart and vessels. This is attended with disturbances of the central nervous system, as profound circulatory disturbances always are.

The astringent and irritant local effects of the salts of some of the metals are utilized therapeutically, but the systemic effects just mentioned are of toxicologic, rather than therapeutic, interest.

LEAD

The systemic effects of lead are of little or no therapeutic importance but they are of toxicologic interest.

Acute lead poisoning is not observed frequently, but a single large dose of one of the lead salts may cause gastro-intestinal irritation with nausea, vomiting and diarrhea, which may be bloody, or constipation with pain, and in exceptional cases these symptoms may be followed by collapse. The acute symptoms are said, in rare instances, to be followed by chronic poisoning.

Chronic lead poisoning is said to be the commonest of all forms of metallic poisoning owing to the widespread use of the metal and its constant absorption with slow elimination.

It is stated that workers in more than one hundred trades are liable to lead poisoning, especially where suitable precautions are not observed. Dust should be avoided as much as possible in lead works, work rooms should be ventilated thoroughly, and workmen

should avoid putting their hands in their mouths or holding articles between their teeth. Food should not be kept where it can be contaminated with the dust arising from the metal work, and clothes should be changed when the workmen leave the work room.

Painters and other workers in white lead are said to be most frequently attacked, and lead smelters, plumbers, typesetters, electricians, potters, enamel ware workers and dyers are affected frequently.

The use of new lead pipes for conveying drinking water is said to be a common source of plumbism, but this is probably less dangerous than is popularly supposed, for the city of New York requires that lead pipes be used to connect houses with the public water mains, and poisoning seldom results from the use of this water.

Wall paper, solder used in sealing canned foods, and even hair dyes are said to be sources of lead poisoning. The cosmetic known as flake white (lead carbonate) is sometimes responsible.

Nausea and loss of appetite with a metallic taste in the mouth are among the earliest symptoms of chronic lead poisoning. A bluish line may appear on the margin of the gums but this may be absent when the mouth and the teeth receive proper attention. Anemia is also an early symptom and it may be the only one to attract attention. Sollmann states that at first there may be a pallor due to a constriction of the cutaneous vessels and later a diminution of the hemoglobin and the number of red blood corpuscles. The red blood cells frequently undergo granular degeneration, the granules staining with basophil dyes. If there is extensive destruction of the red cells there may be jaundice and highly colored urine. This granular degeneration of the red cells is characteristic, and may afford the first clue to the nature of the disease.

Amenorrhea is not infrequent in women so poisoned and lassitude and weakness are frequently observed.

Lead is said to cause gout or a predisposition to it in regions where gout is prevalent.

It is well known that abortion is a frequent result of lead poisoning in pregnant women, and Cushny states

that abortion is common among women workers in lead even when they do not show other symptoms of plumbism. Children born to parents either of whom suffers from chronic lead poisoning are weak and seldom live to reach adult life.

Various manifestations of lead poisoning are due to its actions on peripheral nerves, but the central nervous system may be concerned in certain of these manifestations. Lead causes a general peripheral neuritis affecting both motor and sensory nerves, but certain groups of nerves are much more frequently affected than others, and colic, wrist-drop, anesthesia or excessive tenderness of the skin, arthralgia and disturbances of vision are among the most frequent effects of the actions on the nerves.

Colic is among the most constant symptoms of chronic lead poisoning and Bastedo cites Starr to the effect that it precedes palsy in more than 90 per cent. of the paralytic cases. The attacks come on suddenly, the paroxysms alternating with periods of relative comfort. During the paroxysms the abdominal muscles are tense and hard, the patient often lies face down and obtains some relief by pressing his fists against the region of the umbilicus where the pain appears to be localized. The colic is usually accompanied by obstinate constipation and attacks of vomiting, but occasionally there is diarrhea. The paroxysms of colic are due to spasm of the intestinal wall, but the precise mechanism by which the spasm is induced is not known with certainty. Sollmann attributes it to a stimulation of the nerve endings (vagus) in the intestine as it lacks the peristaltic nature of ganglionic stimulation and it sometimes yields to atropin, which paralyzes the vagus endings.

The intestinal spasms are attended with high blood pressure, which Sollmann also explains as being due to pressure exerted on the splanchnic vessels, whereby the blood is forced into the peripheral circulation.

The paralysis of the extensor muscles in the forearm is also fairly characteristic of chronic lead poisoning. The middle and ring fingers are usually involved before the thumb and index and little fingers, the

wrist being affected later, the condition being commonly termed wrist-drop. The neuritis may be followed by degeneration that extends to the cord and this is followed by rapid atrophy of the extensors, when the unopposed contraction of the flexors gives the hand a claw-like appearance.

Bastedo states that the general peripheral neuritis may be similar to that resulting from alcohol and that it may at least superficially resemble locomotor ataxia.

Among the sensory disturbances are anesthesia, which sometimes begins suddenly and disappears after a few days, or there may be intense pain in certain joints and muscles near them, or great tenderness over different areas of the skin.

Various disturbances of the brain are described under the title of saturnine encephalopathia; these include intense headache, vertigo and mental depression, but these manifestations are said to be rare when the earlier stages of chronic lead poisoning are treated properly.

Lead shares with other metals their irritant actions on the kidneys, and nephritis is a constant result of chronic lead poisoning; lead may possibly induce arteriosclerosis.

Prophylaxis is of the first importance with reference to lead poisoning, but it is not always possible to foresee when one will suffer from its effects, since many escape under conditions that lead to poisoning in others.

Persons who suffer from anemia or general ill health, and those who have suffered from lead poisoning are especially susceptible to its effects. Those who are exposed to the effects of lead have been advised to take very dilute sulphuric acid with a view to converting any of the metal that may be swallowed into the relatively insoluble sulphate, but this should not be permitted to give a false sense of security and cause the neglect of more important prophylactic measures, and it cannot be understood too well that the insolubility of a substance in water does not necessarily mean that it is not absorbable from the gastrointestinal tract.

An overdose of a soluble lead salt frequently causes vomiting that serves to remove practically all of the poison from the stomach, thus preventing further symptoms, but even in such cases it is well to give a dose of magnesium sulphate and wash the stomach in order to remove the resulting sulphate of lead, after which a second dose of magnesium sulphate may be administered with a view to inducing purgation and removing any of the lead that may have escaped from the stomach into the duodenum.

In the absence of sulphate of magnesium or sulphate of sodium one may administer egg-white or milk in order to form the insoluble albuminate of lead, but in any case the precipitate must be removed as promptly as possible. If vomiting and diarrhea have already resulted from the local action of the lead, magnesium sulphate may be administered in order to convert any remaining lead into the sulphate and hasten its passage through the intestinal tract.

Those who work in trades in which lead poisoning is an ever-present danger should be instructed to consult a physician on the appearance of the earliest symptoms such as the metallic taste in the mouth and the loss of appetite.

When a diagnosis of chronic lead poisoning is made one should not be content to find a single source of the intoxication, but owing to the frequency with which minute amounts of lead find entrance into the body from such a variety of sources, the physician should exercise especial care to exclude all sources of poisoning, for a lead worker having become poisoned through the pursuit of his trade may at the time be absorbing minute amounts from other sources. These minute amounts might be harmless to one in good health but might be extremely injurious to one already suffering from the effects of the metal.

The treatment of chronic plumbism includes the relief of symptoms and elimination of the poison.

Atropin paralyzes the vagus endings in the intestine abolishing the intestinal spasm, and with it a non-irritant evacuant, preferably a saline, should be used to empty the bowel. An excessively high blood pres-

sure independent of that caused by the mechanical pressure on the splanchnic-vessels is apparently concerned in the colic, and a vasodilator, such as amyl nitrite, frequently affords relief.

Since the local action of atropin is desired in such cases it would seem better to administer it by the mouth in order that it may reach the nerve endings in the maximum concentration. Since, however, the intense vagus stimulation (if indeed that is the cause of the spasm) may also cause spasm of the pylorus and interfere with the passage of the drug into the intestine after its oral administration, it may be necessary to inject the drug subcutaneously. Even in that case one may fail to elicit the full effect on the nerve endings, not only because of its greater dilution in the general blood stream but because the anemia attending the intense splanchnic constriction interferes with the drug's reaching the endings in the intestine. In such a case it would seem logical to give amyl nitrite by inhalation or nitroglycerin subcutaneously, followed immediately by atropin intramuscularly. If a single dose of atropin (1 mg. or $\frac{1}{60}$ grain) does not relieve, it may be repeated once or even twice.

Opium or morphin may be required for the relief of the intense pain attending the paroxysms of colic and for the relief of the joint pains that usually come later in the course of poisoning. Gout occurring at such times requires the same treatment as that arising under other conditions.

Lead, like other metals, is excreted in part by the kidney, but mainly by the intestine, and while it is stated that the intestinal epithelium participates in the excretion, the fact that the metal is stored more abundantly in the liver than in the other tissues suggests that that organ is responsible for the elimination of the larger part of that remaining in the body after absorption has ceased.

Potassium iodid has long been used to hasten the elimination of the metal, but it seems probable that it has little effect on the excretion of the metal stored in other parts of the body, though it may lower blood pressure and assist the action of diuretics.

Diuretics are also commonly used to hasten elimination and while they, too, have probably but little effect on the elimination of the metal stored in other parts of the body, they may lessen the local action on the kidneys by hastening the process of elimination of that actually stored in them.

The foregoing discussion might lead one to suppose that the diagnosis of chronic lead poisoning is comparatively easy. While it is an extremely simple matter in typical cases, there are many cases presenting such obscure symptoms that the diagnosis will tax the ingenuity of the most careful physician to the utmost. It must be remembered that traces of lead may be found in the urine and feces of persons in health, and that while its detection in the excreta of persons presenting other characteristic symptoms is strong evidence of chronic plumbism, the detection of traces of lead in the urine and feces cannot be accepted as conclusive proof of poisoning by it.

The systemic actions of bismuth, copper, silver and zinc are of some toxicologic interest but they do not require detailed discussion here.

Numerous attempts have been made to utilize the systemic effects of colloidal metals, colloidal silver having been exploited widely as a systemic germicide and antiseptic. The use of colloidal copper has also been suggested, but the results are not encouraging.

(The therapeutic uses of lead salts are mentioned in the discussion of astringents.)

IRON

The normal human body contains some 3 gm. (45 grains) or less of iron, the greater part being present in the hemoglobin of the blood. It is generally stated that only a few milligrams of iron are eliminated from the body daily in the feces and urine, this loss being made good from the iron contained in the food. It is supposed that roughly one-tenth of the hemoglobin of the blood is destroyed daily, the pigments being eliminated in the bile, but the iron is evidently utilized again and again in the formation of hemoglobin, the absorption of extremely small amounts sufficing to make good the loss already mentioned. It is seldom

that the normal diet contains an insufficient amount for the daily needs, but in disease there is often a disturbance of metabolism which prevents the utilization of the iron of the food and additional supplies are required to be administered therapeutically.

Iron has long been used empirically in anemia, but its rational use dates from 1746, when it was discovered that it is a constituent of the red blood corpuscles. Since then there have been many investigations intended to show the form in which iron is taken into the circulation and in which it is utilized in the formation of hemoglobin.

Bunge believed that only those forms of iron which exist in the food, such as meats and vegetables, were absorbed and he suggested that in the form of nucleoalbuminates they escaped conversion into the insoluble sulphid in the intestine, but that, under certain pathologic conditions, even these might be attacked by the hydrogen sulphid in the intestine, and their absorption prevented. He suggested further that in such conditions the administration of ferrous carbonate, or other inorganic salts of iron, would serve to prevent the action of the hydrogen sulphid on the iron of the food, which would then undergo absorption, as usual.

This theory of Bunge's is no longer held by physicians or pharmacologists, but it is still urged by certain interested manufacturers as the basis for their claims for the value of their preparations. On this basis is urged the use of preparations of manganese which are employed in anemia, as it is claimed that the manganese unites with the hydrogen sulphid, thus sparing the iron of the foods for absorption. One need only remember that iron is absorbed mainly in the duodenum and that there is no hydrogen sulphid in that part of the intestine, to recognize that administration of manganese can not affect the absorption of iron.

Bunge calls the iron which exists in the yolk of egg hematogen, and this is evidently the source of iron in the blood of the chick. One manufacturer placed a preparation on the market under the name of hematogen, but Bunge distinctly states that it is a waste of money to buy this expensive preparation.

Schmiedeberg isolated an iron compound from the liver of the pig, supposing this to be the immediate precursor of the iron in hemoglobin. While this may be the form in which iron exists immediately before it is built up into hemoglobin, there is no evidence that it is absorbed any better than other forms of iron.

Tartarkowsky bled animals repeatedly until they were unable to regenerate hemoglobin from stores of iron in the body, and fed some of these animals food free from iron, and others the same food with the addition of inorganic iron salts.²⁸ Those which received the iron with their food regenerated their blood and recovered their normal condition; those which did not, succumbed to the effects of the hemorrhage.

He also found that when animals which had been bled in this way received food containing an abundance of iron they regenerated hemoglobin as well as others which received similar food with the addition of inorganic iron, showing that in simple anemia organic iron in abundance suffices for the restoration of the blood. It seems probable that when the food does not contain an *abundance* of iron the addition of inorganic iron may be of benefit in simple anemia.

It is significant at least that widely different forms of vegetation are capable of supplying the animal organism with all of the iron which it requires for regenerating hemoglobin, and as this iron is almost certainly broken down before it is absorbed, we must suppose that both organic and inorganic forms may be utilized by the body for building up hemoglobin, but only careful clinical experience will determine which of these is preferable for therapeutic use.

At best there can be little difference between the organic and inorganic forms so far as their utilization is concerned, and clinical experience has, as yet, failed to indicate any advantage of one over the other in this particular.

28. Those salts of iron which are precipitated by ammonium sulphid at room temperature are called "inorganic," regardless of whether they contain organic material or not, iron albuminate and peptonate, salts that are not directly precipitated by ammonium sulphid, being classed as inorganic, or preferably, "masked."

The results of various experiments indicate that an amount of iron equal to about 5 mg. ($\frac{1}{10}$ grain) is excreted daily in the intestine and about 1 mg. ($\frac{1}{60}$ grain) in the urine, and it is evident that the diet should contain at least as much as is eliminated. It is in agreement with these estimates that Stockmann found that the normal daily diet of several healthy persons averaged about 8 to 10 mg. ($\frac{1}{8}$ to $\frac{1}{6}$ grain) of iron, while the diet of two chlorotic females contained from $1\frac{1}{2}$ to 3 mg. ($\frac{1}{40}$ to $\frac{1}{20}$ grain).

The following table adapted partly from Bunge and partly from Stockmann, shows approximately the amounts of iron which various foods contain. Sugar, cream, butter, and white of egg are practically iron-free.

IRON CONTENT OF FOODS READY TO SERVE

	Mg.	
1 teacupful of boiled oatmeal.....	0.2 to	0.5
Two apples or oranges.....	0.1 to	0.5
500 gm. (about 1 pound) of grapes.....	0.4 to	1.0
Yolk of two eggs.....	2.0 to	5.0
500 c.c. (about 1 pint) of milk.....	1.0 to	1.5
500 gm. of white bread.....	2.5 to	5.0
500 gm. of whole wheat bread.....	5.0 to	15.0
1 teacupful of mashed potato.....	0.3 to	1.5
1 teacupful of boiled cabbage.....	0.5 to	3.0
1 teacupful of boiled carrots, peas or beans.....	0.5 to	2.0
1 teacupful of boiled spinach.....	3.0 to	15.0
500 gm. "blut-wurst".....	50.0 to	125.0
100 gm. yellow ox-marrow (dried).....	4.0	
100 gm. red calf-marrow (dried).....	8.7	
100 gm. roast beef.....	4.0 to	12.0

The foregoing table shows that the normal diet need not contain an insufficient amount of iron, but it is not always convenient to order a diet for an invalid which will contain an abundance of it, but when ox-marrow, red meats, eggs, whole wheat bread, spinach or "blut-wurst" can be taken there will be no difficulty in supplying the normal daily needs. Hazel nuts, almonds and *green* vegetables are relatively rich in iron.

THERAPEUTIC USES

The use of copperas, or ferrous sulphate, as a disinfectant has been mentioned, and the astringent uses of iron will be considered later. Iron is used in various conditions attended with anemia, being especially useful in those cases in which the red blood corpuscles

individually contain less than the normal amount of hemoglobin.²⁹ There are few therapeutic facts that are better established than that iron is useful in chlorosis, and it is also apparently beneficial at times in secondary anemias. Organic iron is sometimes found to cause less gastric disturbance than the inorganic forms.

Owing to the uncertainties concerning the most absorbable forms of iron one might suppose that the intravenous injection of iron is indicated in those cases in which the oral administration is not followed by improvement, but it must be remembered that iron is extremely poisonous when administered intravenously, and when the oral administration is without results this is probably due to an inability to utilize the iron in the formation of hemoglobin, rather than to any want of iron in sufficient amounts in the blood-building organs. We have no reason, therefore, to suppose that intravenous injections are ever indicated.

It is said that the anemia of ankylostoma yields readily to treatment with iron. One writer records observations on more than 300 cases and states that reduced iron, ferric chlorid, and ferrous sulphate gave better results than organic iron compounds. Iron has been used in numerous conditions in addition to those mentioned, but without sufficient evidence of any beneficial action.

It has long been taught that moist ferric hydroxid is an antidote for arsenic if it be given while the arsenic is still in the stomach, as iron and arsenic react to form an insoluble compound which should be removed as soon as possible. Later experiments seem to show that this procedure is of doubtful value, as the arsenical compound seems to be broken down and the arsenic to be absorbed about as promptly as when no iron hydroxid is given. If the stomach is washed promptly, the antidote is probably of value, as the stomach then contains little but water (if that be used for washing it), and, as previously stated, the arsenic is rendered insoluble in water. When the stomach cannot be

29. William Hunter states that the stored iron in the body is more commonly deficient, and the cause of chlorotic anemia, in the young than in patients in whom the disease occurs after 30.

emptied promptly, however, the iron is probably worse than useless.

DOSAGE

It is obvious that the dosage of iron usually bears little relation to the amount which it is expected will be utilized in the formation of hemoglobin, and the amount administered is frequently regulated with reference to the tolerance shown by the stomach. There is little correspondence between the amounts of iron present in the doses of the different salts as commonly administered: for example, the dose of reduced iron is given as 65 mg. (1 grain) but larger doses are frequently used, whereas the average dose of the syrup of ferrous iodid contains less than one sixth as much iron as the average dose of reduced iron.

The dose of ferrous carbonate is 0.25 gm. (4 grains); of the pills of ferrous carbonate (Blaud's pill) two containing 0.06 gm. (1 grain) each of ferrous carbonate, are taken; of ferrous sulphate, 0.2 gm. (3 grains); of the dried ferrous sulphate two thirds as much as of the crystalline; of the syrup of ferrous iodid, 1 c.c. (15 minims); of iron and ammonium citrate or of soluble ferric phosphate, 0.25 gm. (4 grains); of the tincture of ferric chlorid, 0.5 c.c. (8 minims).

The well-known disadvantages of inorganic salts of iron, such as the difficulty of preventing the oxidation of the ferrous and the astringency of the ferric; the tendency of many of them to injure the teeth; the difficulty of securing absorption and their tendency to disturb the stomach, have led to the introduction of a very large number of official and unofficial, galenical preparations, while the numerous theories advanced with regard to the form of iron which is utilized directly in the formation of hemoglobin have resulted in the introduction of numerous proprietary preparations of iron, and of manganese intended as substitutes for iron, but there is not the least evidence that any of these proprietary preparations,³⁰ even those

30. Examples of the way in which some of the proprietary preparations of iron or its substitutes are exploited are discussed in *Jour. Am. Med. Assn.*, Sept. 23, 1905, p. 934; April 6, 1907, p. 1197, and April 23, 1910, p. 1389.

sponsored by eminent investigators, have any advantage over the preparations enumerated below.

MATERIA MEDICA

Ferrum.—Iron, U. S. P., is used in pharmacy in the production of preparations of iron, but in medicine it is used chiefly in the form of:

Ferrum Reductum.—Reduced Iron, U. S. P., the official product of which should contain not less than 90 per cent. of pure metallic iron. It occurs as a grayish-black lustrous powder, without odor or taste, that is permanent in dry air. It is insoluble in water or in alcohol and is preferably administered in capsules or in the form of recently prepared pills.

Of the many salts of iron that occur, the following ferrous combinations are, perhaps, the most widely used:

Ferri Carbonas.—Ferrous Carbonate, U. S. P., is usually made by the interaction of ferrous sulphate with a soluble carbonate and is used in medicine chiefly in the form of:

Massa Ferri Carbonatis.—Mass of Ferrous Carbonate, U. S. P.—This mass, better known as Vallet's mass, is a mixture of ferrous carbonate with honey and sugar to form a mass and to act as a preservative. The average dose of 0.25 gm. (4 grains) contains approximately 0.1 gm. ($1\frac{1}{2}$ grains) of ferrous carbonate.

Mass of ferrous carbonate is frequently prescribed in combination with strychnin or nux vomica or with arsenic trioxid. The following is a typical combination:

	Gm. or c.c.	Grains
R Massa ferri carbonatis.....	6	100
Extracti nucis vomicae.....	0 40	6
vel		
Strychninae	0 02	$\frac{1}{3}$
M. et fiat pilulas No. 20.		

Pilulae Ferri Carbonatis.—Pills of Ferrous Carbonate, U. S. P., popularly known in Bland's pills, consist of a mixture of freshly formed ferrous carbonate and potassium sulphate with sugar and a smaller

proportion of tragacanth and althea to make a mass. Each pill represents approximately 0.06 gm. (1 grain) of ferrous carbonate. They should be freshly prepared.

Ferri Sulphas.—Ferrous Sulphate, U. S. P., and the dried product.

Ferri Sulphas Exsiccatus.—Exsiccated Ferrous Sulphate, U. S. P., are seldom employed for internal administration but are used indirectly as the source of ferrous iron in the preparations of ferrous carbonate enumerated above.

Ferri Iodidum.—Ferrous Iodid, U. S. P., is commonly used in medicine in the form of the syrup.

Syrupus Ferri Iodidi.—Syrup of Ferrous Iodid, U. S. P., contains about 5 per cent. by weight of FeI_2 . It occurs as a transparent, pale green or yellowish green liquid having a sweet, but strongly ferruginous taste and an acid reaction.

Syrup of ferrous iodid is incompatible with alkali carbonates, acid salts and vegetable astringents. It is very susceptible to oxidation and is best kept in small well-sealed vials exposed to diffuse daylight. Syrup of ferrous iodid is preferably directed to be administered alone, well diluted with water. It should not be used when a reddish or yellowish color has developed, indicating that oxidation has taken place.

Of the many ferric salts and combinations that have been suggested from time to time the following are fairly representative:

Ferri et Ammonii Citras.—Iron and Ammonium Citrate, U. S. P., a scale salt containing ferric iron and ammonium citrate corresponding in amount to not less than 16 per cent. of metallic iron. It occurs as thin, transparent, garnet-red scales, odorless and having a saline, mildly ferruginous taste. The compound is deliquescent in moist air and is readily and completely soluble in water but is insoluble in alcohol.

Ferri Phosphas Solubilis.—Soluble Ferric Phosphate, U. S. P., a compound containing ferric phosphate corresponding in amount to not less than 12 per cent. of metallic iron. It occurs as thin, bright green,

transparent scales, odorless, and having a saline, slightly acidulous taste. The salt is permanent in dry air when excluded from light but when unprotected soon becomes dark and discolored. It is freely and completely soluble in water but insoluble in alcohol.

Like other soluble salts of iron, these scale salts are incompatible with fixed alkalies, alkali carbonates, and vegetable astringents. They may be administered in either water or syrup, with or without the addition of a small amount of alcohol and a trace of aromatic oil.

Ferri Chloridum.—Ferric Chlorid, U. S. P., is used in medicine principally in the form of:

Tinctura Ferri Chloridi.—Tincture of Ferric Chlorid, U. S. P., a hydro-alcoholic solution of ferric chlorid, FeCl_3 , containing not less than 13.28 per cent. of anhydrous salt, corresponding to about 4.5 per cent. of metallic iron. Tincture of ferric chlorid occurs as a bright brownish liquid having a slightly ethereal odor, a very astringent taste and an acid reaction. On exposure to light it is gradually reduced with the production of some ferrous salt, hence it should be carefully preserved in glass-stoppered bottles, protected from the light. Because of its objectionable styptic taste and distinct acid reaction it is now seldom employed internally. When so given, care should be taken to protect the teeth either by directing that the diluted tincture be taken through a glass tube or that the mouth be carefully rinsed with a slightly alkaline mouth-wash immediately after taking the medicine.

MERCURY

When the soluble mercuric salts, such as the chlorid, are taken they may be brought into more intimate contact with the tissues than the insoluble salts, such as calomel. This is because the solutions of the mercurials permit the formation of the albuminate, which is soluble in excess of albumin, such as exists in the tissue fluids.

The solubility of the mercurial compound formed, and its toxicity for all cells with which it comes into contact in sufficient concentration permits it to exert its toxic action not only on the mucous membrane of

the alimentary tract at the time it is swallowed, but also on the cells of the renal tubules and of the intestine which participate in the excretion of the metal.

It is commonly stated that a metallic taste and a burning sensation in the mouth and throat are the first symptoms observed after a toxic dose of mercuric chlorid has been swallowed. Animals, however, appear to suffer no discomfort after the introduction of mercuric chlorid through a stomach-tube before the onset of nausea, which is promptly followed by emesis. The vomitus may be tinged with blood within a few minutes after the administration of an excessive dose, showing the rapidity of the onset of the corrosive action. The vomiting may be almost incessant or there may be intervals during which an animal gives little sign of actual discomfort. A cat vomited fourteen minutes after the administration through a stomach tube of a 1:500 solution containing an amount of the mercuric chlorid corresponding to about 2 gm. (30 grains) for a man. Another cat received about one tenth as much in a 1:5,000 solution and though this amount corresponds to an almost certainly fatal dose in man the animal did not vomit or exhibit any symptoms of discomfort during more than forty-eight hours that it was under observation. In man, the onset of nausea and vomiting may be sufficiently delayed to permit notable amounts of the poison to pass into the duodenum, where part of it is absorbed. The remainder being carried into the large intestine causes diarrhea in some cases, but in others this result is delayed for twenty-four hours, that is, until the irritant action of the metal is exerted on the intestinal cells during excretion. The evacuations often resemble those seen in arsenic poisoning, and contain blood and shreds of desquamated intestinal epithelium.

Excessive doses of mercuric chlorid may cause profound collapse through the severity of the gastrointestinal action. Death may result in a few hours, but the patient usually lives from three to eight days after a fatal dose has been taken, and death may then be due to collapse incidental to the action on the central nervous system and to gastro-intestinal and renal

effects. There is little direct action on the heart and central nervous system in many cases, and consciousness is commonly retained in acute poisoning until shortly before death, when uremic symptoms with coma result.

Aside from the salivation resulting from the nausea that comes on soon after the poison has been taken, there is sometimes an intense activity of the salivary glands. The saliva containing mercury, which is irritant, may occasion excoriations and deep ulcerations extending even into the bone of the jaw unless care is given to the mouth. A 2 per cent. solution of potassium chlorate is recommended as a mouth-wash in such cases.

The salivation and soreness of the gums and mouth are important as they are among the earliest of the symptoms commonly observed in chronic mercurial poisoning when mercury is taken over prolonged periods, or when persons are exposed to its action as in the trades in which it is used (mirror makers).

In severe mercurial poisoning the colon and cecum are commonly the seat of ulceration caused by the direct action of the salt before its absorption, or more commonly, during excretion. The small intestine suffers comparatively little, probably because the poison does not remain in it long, but is either absorbed or passed on into the cecum.

The urine may be increased for a time and later completely suppressed, partly through the action of the mercury on the epithelium of the tubules, partly through the circulatory changes induced by the watery diarrhea. This by withdrawing fluid from the blood increases its viscosity, which with the lowered blood pressure causes further interference with the renal secretion.

Attention has been called to the necessity for preventing diarrhea when calomel is administered for its diuretic action, and the reasons for this have been explained. It is in keeping with that explanation that when mercurial poisoning is attended with severe gastro-intestinal disturbances with watery diarrhea, there should be less nephritis than when poisoning of

equal severity is accompanied with comparatively little diarrhea.

The various skin lesions observed during chronic mercurial poisoning are due to the irritation caused during excretion in the sweat.

In chronic poisoning in long-standing cases (not in those induced by the therapeutic use of mercury), muscular tremors of central origin may occur, and a condition of erethism, or increased excitability of certain parts of the central nervous system is described. This erethism is characterized by irritability and alterations in the disposition.

The milder forms of chronic mercurial poisoning are induced when any of the mercurial is given over a prolonged period in the treatment of syphilis, and, indeed, the beginning of these symptoms serves as a guide in limiting the administration. More severe symptoms occur among workers in trades in which mercury is used constantly. The continuous administration of calomel is said to give rise to severe stomatitis more frequently than is the case with mercuric chlorid and other soluble salts of mercury, because it is impossible to control the absorption with any degree of precision in the case of calomel. Undue absorption thus occurs at times, especially when opium is administered to control the diarrhea which calomel causes otherwise.

Acute fatal poisoning with mercuric chlorid has become quite common of late, owing to carelessness or the deliberate use with suicidal intent of the "antiseptic tablets," each of which contains about 7 grains of the poison.

There is little doubt that the widespread use of these tablets in solution for preventing conception is responsible for their being present in many households, inviting mistakes and affording opportunities for self-destruction.

Various ways have been suggested by which mistakes with the tablets will be rendered impossible, thus, it has been recommended that they be made of cylindrical shape, or that they be colored distinctly with indigo or ultramarine blue. The distinctive shape

is preferable, since mistakes are often alleged to be due to taking tablets in the dark. The tablets are threaded together like beads by one manufacturer.

Fatal poisoning also results occasionally from the use of solutions of mercuric chlorid as a wash for large wounds and body cavities, and it should be remembered that absorption may take place from any mucous or denuded surface. Fatal poisoning has even followed the local application of the mercurial ointment, though this is extremely rare. It is even said that the oral administration of calomel may be followed by absorption and the typical corrosive action of mercuric chlorid, but this must also be rare.

The stomach should be emptied as promptly as possible after a poisonous dose of mercuric chlorid has been swallowed. The stomach tube is preferable for this purpose,³¹ for while emesis occurs in the large majority of cases from the action of the drug, this is not sufficiently prompt to prevent the absorption of notable amounts, or to prevent still larger amounts from passing into the duodenum.

Egg-white, milk or other readily available form of protein should be administered immediately but not too freely, even before the stomach-tube is passed, and again after the stomach has been emptied as thoroughly as possible. The portion administered at first is intended to precipitate the poison and stop its further action on the stomach, and that administered after the stomach has been washed is for the purpose of protecting the mucous surface and precipitating any mercuric chlorid that may have escaped precipitation in the first case.

Immediately after washing the stomach, 30 gm. (1 ounce) of magnesium sulphate should be dissolved in 500 c.c. (1 pint) of water and administered in order to dilute any of the poison that passes into the duodenum and to hasten its evacuation in the feces. Egg-white or milk may be added to this solution in order to precipitate any mercuric chlorid that may exist in

31. The danger of perforating the stomach, while attempting to pass the stomach-tube after corrosives have been swallowed, has probably been much exaggerated. Of course, one should exercise caution in passing the tube under any conditions.

the alimentary tract, and egg-white or milk should be administered from time to time for the same purpose.

One cannot be certain that the most energetic treatment will suffice to prevent the absorption of a poisonous dose of the salt, hence attention should be given to its elimination and to the treatment of symptoms that may arise. Since mercury is eliminated by all of the channels of excretion, it would appear to be logical to promote all the secretions so far as possible, and diaphoretics and diuretics should be used freely.

Attention has been called in previous chapters to the copious diuresis that may be induced by the intravenous injection of large amounts of a 2 per cent. solution of sodium sulphate. While this procedure is not justified by the mere suspicion that a toxic dose of mercuric chlorid may have been absorbed, it would probably prove beneficial if used early in the course of poisoning after absorption has taken place and before severe nephritis has developed. We are not aware of any case of mercurial poisoning having been so treated, but when a fatal outcome appears almost certain in the presence of the usual methods, it would at least seem justifiable to employ any means of hastening the elimination that does not jeopardize the patient's welfare.

The diarrhea and its attendant pain that result during the excretion of mercury may require the administration of opium, but the evacuations must not be checked altogether since that would prevent the elimination of the poison.

It is often asserted that potassium iodid facilitates the elimination of mercury from the body but no satisfactory evidence exists that it exerts any marked effect in this way.

THERAPEUTIC USES

The disinfectant, diuretic and cathartic actions of mercury have been discussed. Its use in syphilis remains to be considered.

In this disease its value has been established beyond question. Its well-known disadvantages and the overshadowing literature of salvarsan, however, together

with the sensational introduction of the latter as a cure for syphilis have tended of late to create the impression that mercury is of only secondary importance. In truth mercury is indispensable still, even though there are some cases of syphilis which may possibly yield to arsenical treatment, for mercurial treatment becomes necessary in the larger proportion of cases. It seems probable that it will be used more and more in conjunction with arsenic when the technic of their combined use is perfected.

Preference has been given at one time or another to nearly every one of the better-known salts of mercury, including those that have been introduced in the effort to overcome some of the disadvantages of the other mercurials. The value of mercury in the treatment of syphilis depends on getting enough of it into the circulation to destroy (or to enable the body to destroy) the *Spirochaeta pallida*, the causative organism. Since mercury is toxic to all of the cells of the human body with which it comes in contact in sufficient concentration, it follows that whatever method of administration is chosen the toxic effects of the metal must be exerted at the points of absorption and elimination. It is therefore apparently impossible to secure the therapeutic action of mercury without at the same time subjecting the patient to some of its disagreeable side actions.

The literature dealing with the treatment of syphilis and the best methods of administering mercury is extensive, but the general practitioner will usually depend on oral administration despite its many disadvantages, until better means of administering the remedy are perfected. Many specialists prefer the intramuscular injection of an insoluble salt such as the salicylate, as a sufficient quantity can be given at two injections to produce an influence which will last a week, thus saving much time. This method, however, has the great disadvantage of resulting in a variable rate of absorption, so that the dosage cannot be regulated satisfactorily. The pain attending the injection is said to be less severe but to last longer than that following the injection of mercuric chlorid. A few

specialists prefer the mercuric chlorid for intramuscular injection. It has the advantage of insuring rapid absorption with satisfactory regulation of the dosage, but it causes severe pain and the injections must be made every day.

Inunction is practiced in some institutions where the services of trained attendants are available. The ointment of mercury is rubbed into the various parts of the body successively. It is extremely untidy and it gives rise to much discomfort.

Mercurial vapor baths would appear to have decided advantages were it possible to regulate the dosage satisfactorily.

Calomel, mercury and chalk, mass of mercury, and the "proto" or yellow iodid are insoluble forms of mercury that may be administered by the mouth in pills or capsules. They all cause diarrhea, usually necessitating the use of opium to secure sufficient absorption, and they have the disadvantage of being variable in absorability even then.

Mercuric chlorid, or red mercuric iodid may be given in solution. Mercuric chlorid and potassium iodid are commonly prescribed together, the soluble double salt of mercury and potassium iodid being formed.

When arsenic is used in the treatment of syphilis an effort is made to destroy all of the spirochetes in the blood with one dose. It would therefore seem logical to use the largest doses of mercury that the patient can stand in order that the micro-organisms may be destroyed as rapidly as possible, but the toxicity of mercury for the host and its many side actions are so important that they must be taken into consideration in the method of treatment. A lack of agreement also exists concerning the best methods of procedure with the various mercurials.

The administration of mercurials during the latter months of pregnancy may induce abortion, or the newborn may suffer from chronic mercurial poisoning. The simultaneous occurrence of syphilis and tuberculosis offers additional difficulties in the administration of mercury but it does not wholly contraindicate its use.

Mercurial ointment is also used for destroying parasites, especially body lice, but there are other methods that are equally effective and more cleanly. A solution of mercuric chlorid, 1:500 in vinegar, diluted acetic acid or diluted alcohol may be applied cautiously; but absorption may occur if too much of the solution is used, hence not more than one fluidounce of such solution should be applied during a day.

Ointment of ammoniated mercury is antiseptic and a local stimulant; it is used to excite a healthy inflammatory reaction in psoriasis, and it is also applied to areas of suppurating dermatitis.

DOSAGE

The single dose of the various mercurials varies widely with the method employed. Larger single doses of the salicylate are given when injections are made intramuscularly twice a week than of the mercuric chlorid when used daily. On the other hand, it is obvious that the amount of calomel or one of the other insoluble mercurials that will be required to induce a given effect will vary considerably with the measures taken to prevent its rapid removal by purgation. It is probable that the amount of mercury necessary to be absorbed in a given length of time to produce the desired therapeutic effects, that is, the destruction of the spirochete, does not vary nearly so widely as the total amount which may need to be administered.

The oral dose of mercuric chlorid (corrosive sublimate) is 0.002 to 0.01 gm. ($\frac{1}{30}$ to $\frac{1}{6}$ grain) in pill or preferably in dilute solution. Attention is again called to the much greater irritation caused by concentrated solutions than by dilute ones containing equal amounts of irritant salts. The maximum oral daily dose is 0.06 gm. (1 grain). The daily dose by intramuscular injection should not exceed 0.01 gm. ($\frac{1}{6}$ grain).

Solutions of from 1:1,000 to 1:2,000 are used to excite dermatitis and exfoliation; care should be taken to avoid absorption of large amounts, hence such solutions should be used only with caution and they should be discarded should there be evidences of absorption, such as salivation or a metallic taste in the mouth.

It is difficult to state the dose of calomel in exact terms with such strict limitations as in the case of the mercuric chlorid. The administration is regulated rather by the symptoms induced and evidence of absorption than by mere figures. The single dose varies from 0.06 to 0.12 gm. (1 to 2 grains) and from 3 to 5 grains daily until slight mercurialism is induced when it is employed in the treatment of syphilis.

Soluble iodids, such as sodium or potassium iodid, are contraindicated during the administration of calomel as they react with it to form metallic mercury and mercuric iodid.

The yellow mercurous iodid, also called the green iodid, or the protiodid, is little used except for the treatment of syphilis; it has less tendency than calomel to cause diarrhea. It is best administered in pill form after meals in doses of 0.015 gm. ($\frac{1}{4}$ grain) three times daily, increasing gradually by 0.008 gm. ($\frac{1}{8}$ grain) till the symptoms indicate that the limits of tolerance are being approached. The appearance of salivation, diarrhea and pain is the signal for interrupting the administration or diminishing the dose.

Red mercuric iodid is given by the mouth in doses of 0.003 gm. ($\frac{1}{20}$ grain) three times daily. It is commonly prescribed in a liquid form by directing mercuric chlorid and potassium or sodium iodid in solution somewhat as follows:

	Gm. or c.c.	grains i
R̄ Hydrargyri chloridi corrosivi.....	0 06	$\frac{3}{8}$ iss
Potassi iodidi.....	6 00	$\frac{3}{8}$ iiii
Aquae	100 00	

Red mercuric iodid may be injected intramuscularly, in a solution in a bland fixed oil containing from 0.2 to 1 per cent. The daily intramuscular dose is about 0.005 gm. ($\frac{1}{10}$ grain) or 1 c.c. (15 minims) of a 0.5 per cent. solution.

Mercuric salicylate has come into use largely for intramuscular injection suspended in liquid paraffin or other oleaginous menstruum. Of a 10 per cent. suspension, containing 0.06 gm. (1 grain) of mercuric salicylate, 0.6 cc. (10 minims) is injected intramuscularly about twice a week or once in four days.

Mercury with chalk is given in doses about equal to those in which calomel is used. The action of mercury with chalk, the mass and the ointment, containing the metal in fine division, is quite different from that of the metal in mass, since the finely divided globules of mercury are partially oxidized.

Metallic mercury was formerly administered in substance in large doses, but it is seldom given now in the pure form.

MATERIA MEDICA

Hydrargyri Chloridum Corrosivum. — Corrosive Mercuric Chlorid, U. S. P., more popularly known as corrosive sublimate, occurs in the form of heavy colorless crystals or a heavy white powder having an acrid and persistent metallic taste. It is permanent in the air and is quite soluble (1:13) in water and freely soluble (1:3) in alcohol. Ammonium chlorid, sodium chlorid, tartaric and citric acid increase its solubility in water.

Mercuric chlorid is precipitated from its aqueous solutions by albumin, but redissolves in a large excess of the albumin solution. In administering egg white as an antidote this property of albumin should be borne in mind. Mercuric chlorid is also incompatible with soluble carbonates and hydroxids forming insoluble mercuric oxid. With soluble iodids it forms mercuric iodid or complex salts. It is incompatible with many alkaloids and other organic compounds and is reduced to calomel or metallic mercury by iron, zinc and other reducing agents.

Hydrargyri Chloridum Mite—Mild Mercurous Chlorid, U. S. P., more popularly known as calomel, occurs as a white impalpable powder, becoming yellowish-white on trituration with strong pressure. It is odorless, tasteless and permanent in air. Mild mercurous chlorid is practically insoluble in water, alcohol or ether. It undergoes change when exposed to the action of light or under the influence of alkaline chlorids, bromids or iodids; by which mercuric salts are more or less rapidly formed.

For intramuscular injections it may be directed to be suspended in liquid petrolatum or a bland, fixed

oil and the equivalent of 0.1 gm. ($1\frac{1}{2}$ grain) injected once a week.

Hydrargyri Iodidum Flavum—Yellow Mercurous Iodid, U. S. P., also known as protiodid of mercury and popularly, though erroneously, called green iodid of mercury, occurs as a bright yellow amorphous powder that is odorless and tasteless. By exposure to light it becomes darker, in proportion as it undergoes decomposition into mercuric iodid and metallic mercury. It is almost insoluble in water and wholly insoluble in alcohol. Yellow mercurous iodid is usually administered in the form of pills. It is incompatible with oxidizing agents, alkalies and the haloid salts of the alkali metals, which tend to decompose it with the formation of mercuric salts. Alkali iodids decompose mercurous iodid with the formation of metallic mercury and soluble alkali mercuric iodid.

Hydrargyri Iodidum Rubrum—Red mercuric Iodid, U. S. P., popularly known as biniodid of mercury, occurs as a scarlet red powder that is odorless and tasteless. It is permanent in air, and nearly insoluble in water but slightly soluble (1:116) in alcohol; also slightly soluble in fatty oils. Red mercuric iodid may be given internally in the form of solution with potassium or sodium iodid or administered in the form of pills. For intramuscular injections the solution in a bland, fixed oil is frequently used. Mercuric iodid is incompatible with alkalies and their carbonates and alkaloids and their salts. The addition of an alkaline iodid produces a water-soluble complex salt.

Hydrargyri Salicylas—Mercuric Salicylate, N. N. R., occurs as a white amorphous powder, tasteless and odorless and neutral to litmus paper. It is nearly insoluble in water or alcohol but is soluble at the ordinary temperature in solutions of sodium hydroxid or sodium carbonate, with the formation of a double salt. Mercury salicylate is incompatible with iodids. Like the mild mercurous chlorid it is used for intramuscular injections in the form of a suspension (1:10 to 1:20) in liquid petrolatum or other fixed oil, and is administered in doses of about 0.1 gm. ($1\frac{1}{2}$ grains).

Hydrargyrum—Mercury, U. S. P., in its ordinary form is a shining, silver-white, volatile and fluid metal without odor or taste. In medicine it is used at the present time largely in the forms in which it is reduced to a fine state of subdivision. It is capable of absorption either by the skin or mucous membranes and produces the ordinary pharmacologic effects of its salts. Among the several official forms of mercury are:

Hydrargyrum Cum Creta—Mercury with Chalk, U. S. P., a powder popularly known as gray powder, containing 38 per cent. of mercury with clarified honey and prepared chalk. It occurs as a light gray, slightly adhesive powder, with little odor and a slightly sweetish taste. It is insoluble in water but is partially dissolved by diluted hydrochloric acid, the residual mercury being left in a finely divided state.

Massa Hydrargyri—Mass of Mercury, U. S. P., is popularly known as blue mass, and is a mixture containing 33 per cent. of mercury, with glycyrrhiza, althea, glycerin and honey of rose. The mercury should be reduced to such a fine division that globules are not visible under a magnification of 10 diameters.

Unguentum Hydrargyri—Mercurial Ointment, U. S. P., is a mixture of 50 per cent. of mercury with prepared suet, benzoinated lard and 2 per cent. of oleate of mercury. The mercury should be reduced by trituration to such fineness that globules are no longer visible under a lens magnifying 10 diameters.

Unguentum Hydrargyri Dilutum—Blue Ointment, U. S. P., is a diluted mercurial ointment made by mixing approximately 2 parts of mercurial ointment and 1 part of petrolatum.

Hydrargyrum Ammoniatum—Ammoniated Mercury, U. S. P., is a mercuric ammonium chlorid produced by the precipitation of a solution of mercuric chlorid by a solution of ammonia. It should represent not less than 78 nor more than 80 per cent. of metallic mercury. It usually occurs in the form of white pulverulent pieces or a white amorphous powder, having an earthy, afterwards styptic and metallic taste. It is practically insoluble in water or in alcohol.

but is gradually decomposed by washing with water. It is readily soluble in warm acids with decomposition.

Unguentum Hydrargyri Ammoniaci—Ointment of Ammoniated Mercury, U. S. P., is a mixture of 10 per cent. of ammoniated mercury with white petrolatum and hydrous wool-fat.

CHAPTER XII.—DEMULCENTS, EMOLLIENTS, ASTRINGENTS, IRRITANTS AND CAUSTICS

DEMULCENTS, EMOLLIENTS AND OTHER PROTECTIVES

The word "demulcent" is derived from "demulceo" meaning "to smoothen"; the word "emollient" from "emollio" meaning "to soften." Mucous membranes rarely require softening though they sometimes require agents to render their surfaces smoother. When, however, an inflamed skin becomes hard it requires softening, hence we speak of applying demulcents to mucous membranes and emollients to the skin, the same agent usually being both demulcent and emollient. Petrolatum is used for both purposes, but when used internally it is commonly spoken of as a lubricant for the intestinal tract.

Cushny states that the number of demulcents, emollients and astringents in common use might be curtailed considerably without loss to therapeutic practice, and the physician will find that "Useful Drugs" contains all that he needs of this group.

Acacia, tragacanth and other gums are colloidal substances that can be dissolved in water or made to absorb many times their weight of it, forming mucilages that serve to protect mucous membranes against irritants of various kinds. They form a coating that protects the surface mechanically against solid particles, and they retard the movement of liquids that are incorporated with them so that absorption and penetration into the mucous membranes are delayed.

Poisons, such as strychnin, are less active when dissolved in solutions of colloids than when dissolved in water, the slower absorption from the former permitting of the simultaneous excretion of a portion of

the poison. Sweet and sour substances have less taste when dissolved in solutions of colloids than when dissolved in water, because of their slower penetration into the organs of taste in the tongue.

That such dissolved substances are more slowly absorbed, also explains the protective action of demulcents against soluble poisons in the gastro-intestinal tract, but, on the other hand, when such colloid solutions remain too long in contact with inflamed and infected surfaces they offer opportunities for bacteria to develop. This does not apply with so much force to the mouth, nose and throat, in which the natural secretions and frequent washing suffice to remove bacteria, but to the gastro-intestinal tract, where the rapid multiplication of putrefactive organisms together with the delayed digestion of food and absorption of the products of digestion may result in further injury to the inflamed mucous membranes.

Demulcents may be added to solutions of irritant drugs, such as hydrated chloral, to lessen or prevent gastric irritation, thus avoiding emesis and permitting the drug to be absorbed. For this reason they are sometimes added to nutrient enemas, as enemas are prone to set up peristalsis, thus causing their expulsion. The colloids retard or prevent this, affording time for the absorption of the nutriment.

It is sometimes difficult to relieve thirst when the stomach has become so irritable that even small amounts of water are rejected. Demulcents may be added to water in such cases, and when large amounts of water are to be administered by the mouth to induce diuresis, the use of demulcents and flavoring prevents nausea and facilitates the passage of water into the duodenum, where it is absorbed. Albumin water, made by adding the white of an egg to a glass of water with a little lemon juice or barley water, serves the double purpose of introducing water and nitrogenous or carbohydrate food, though the food value may be slight.

Demulcents are also used to allay the irritation of the gastro-intestinal tract in poisoning with such metallic salts as those of mercury. The possibility of bacterial infection should be borne in mind and in such

cases the combination of an antiseptic and colloid is probably preferable. Glycerite of starch serves as a demulcent, but is digested without becoming a nidus for the growth of bacteria. The objection to the use of demulcents in the treatment of diarrhea is the same as in other inflammatory conditions of the intestine. This applies with even greater force when it is evident that pathogenic bacteria are already doing harm. Petrolatum would seem to have a special field of usefulness in such cases, at least on theoretic grounds, but protectives, such as bismuth salts, that are also astringent and antiseptic, are usually preferred for use in combination with the mucilaginous demulcents.

The skin is kept soft and pliable under normal conditions by its natural secretions, but there are innumerable ways in which the pliability is destroyed and it is rendered hard, the hardening being followed by cracking and greater or less irritation. The hands especially are subject to innumerable minor injurious influences such as frequent washing with alkali soap; frequent wetting and drying; the action of cold winds; of various chemicals, including acids and alkalies in various trades; of tannin in vegetables in domestic service; of dust and ashes. Probably the majority of occupations involve a certain degree of injury to the skin of the hands, and while this is not so serious as to demand medical treatment, the frequent use of harmless demulcents adds much to the comfort of many persons.

All bland oils are emollient, but they become rancid on exposure to the air, and ordinarily they are inconvenient to use on the hands unless they are thoroughly rubbed into the skin. Even this may be troublesome; petrolatum for this purpose is quite inconvenient, though commonly used. Many people find glycerin irritant, especially women and children who have sensitive skin. Others find it a most convenient emollient when diluted with at least an equal volume of water. It is applied after washing and wiping the hands but while they are moist. A mixture that has been found useful consists of equal parts, by measure,

of glycerin, water and solution of hydrogen peroxid. Rose water in equal amount may be substituted for the water or a small amount of benzoin or other flavoring may be added.

Among the emollients that do not require detailed discussion, various ointment bases may be mentioned. Lard becomes rancid, hence the pharmacopeia directs that it shall be treated with benzoin, which prevents rancidity. Lanolin, or hydrous wool fat, does not become rancid, but it is not pleasant to use.

Wild reported to the therapeutic research committee of the British Medical Association recently on the availability of certain ointment bases in common use. While the subject is not fully understood, he holds that the fats such as lanolin and lard are absorbed more readily than petrolatum, but that we have little knowledge of the rates at which incorporated substances leave these substances to go into the tissues.

While this has little bearing on the use of ointment bases as demulcents it is obviously important when the use of ointments as a means of applying drugs for their systemic action is considered.

The melting point of the ointment is held to be of first importance, gradual melting being desired, hence Wild prefers a mixture of ointment bases with different melting points.

Certain other mechanical protectives serve the same purpose as the mucilaginous and oily demulcents and emollients; for example, the insoluble salts of bismuth, which are usually taken in a fine powder suspended in mucilage, form a thin layer on the mucous membrane of the stomach and intestine. Dusting powders, such as starch, lycopodium, talcum and boric acid serve much the same purpose on the inflamed skin. The salts of bismuth are usually classified as astringents, among which they will be mentioned later. They do not appreciably dissolve in the gastro-intestinal tract as a rule, but pass through it unchanged exerting their protective action throughout its length.

The subnitrate has long been the most popular of the salts of bismuth, but its popularity over the subcarbonate is apparently due to force of habit, for their

beneficial actions are similar, while the subcarbonate does not cause poisoning as the subnitrate does occasionally. This poisoning is due in part to the absorption of nitrites resulting from the decomposition of large doses of the subnitrate by bacteria, in part to the systemic action of the metal bismuth.

Bastedo administered bismuth subnitrate to dogs and after several hours found the bismuth in a flocculent state coating the mucous membrane very uniformly as far as the ileocecal valve. He also administered bismuth subnitrate with a test breakfast to a patient and at the end of the hour found the salt in a flocculent state and uniformly mixed with the extracted stomach contents. It separated slowly from the food.

Cannon introduced the practice of administering the salts of bismuth and observing their progress through the alimentary tract by means of the fluoroscope, as an index of gastro-intestinal movements. The subcarbonate or the subchlorid is to be preferred to the subnitrate for this purpose because of the danger of using such large amounts of the latter as would be required (60 gm. or 2 ounces).

Bismuth salts are partly converted into the sulphid in the colon and this may act as an irritant; like the sulphids of many other metals it colors the stools black.

The soluble salts of bismuth, such as bismuth and ammonium citrate, are apparently wholly superfluous, as the soluble salts are converted into insoluble ones in the gastro-intestinal tract, and absorption is never desired. Linseed or flaxseed is used in the form of an infusion as a demulcent. The mucilaginous outer wall of the seed swells or dissolves in water to a pleasant tasting mucilage. The crushed or ground linseed is used in the form of cataplasms as an emollient and, because of its property of retaining heat, for the relief of inflammatory conditions generally.

The insoluble salts of zinc, more particularly the oxid and stearate, are used externally in the form of a dusting powder or an ointment to protect the skin and to allay irritation.

To absorb the discharge in eczematous conditions or to check excessive perspiration, mixtures of equal

parts of zinc oxid or zinc stearate with starch and boric acid or one of the insoluble bismuth salts may be used. The composition of such dusting powders should be varied to meet the particular indications or needs.

THERAPEUTIC USES

The therapeutic uses of demulcents are indicated to a large extent by the preceding discussion. Attention has been called to the fact that they retard the absorption of fluids with which they are mixed, and they may check diarrhea by lessening the irritation of the intestinal mucous membrane, thereby diminishing peristalsis and prolonging the time allowed for absorption of fluid so that less passes into the large intestine. The fluid may also be retained so tenaciously by the demulcent, as in the case of compound licorice powder, that the bulk of the intestinal contents is increased and normal peristalsis is stimulated. In this case the laxative action is due partly to the irritation of the mucous membrane caused by the hydrogen sulphid or sulphurous acid formed in the intestine from the sulphur of the powder.

Demulcents are commonly used for the relief of cough and sore throat. It sometimes happens that the continued use of demulcent lozenges causes the tongue to become coated with insoluble matter from the lozenges, and it will be found advisable in such cases to use a gargle or spray for the throat and to wash the mouth with solution of hydrogen peroxid.

The salts of bismuth are used to allay vomiting from gastric irritation and to check diarrhea arising from irritation due to decomposing food; to protect the gastric mucous membrane in hyperacidity and in gastric ulcer; in gastro-intestinal catarrh and in ulcerative enteritis.

Bismuth subnitrate and subcarbonate are used externally for ulcers and suppurating wounds. A paste made of bismuth with petrolatum has long been used in treating old sinuses and fistulous tracts. It is injected once a week in cases of chronic tuberculous cavities but not in acute conditions. Poisoning has resulted from its use in this way and the use of the paste should

be discontinued on the appearance of symptoms indicating that absorption is taking place. These symptoms include headache, nausea, stomatitis, with occasionally a blue line on the gums. In such cases the cavities should be irrigated thoroughly with warm olive oil and filled with the oil, which is allowed to remain for twenty-four hours, after which the washing with the oil is to be repeated daily until symptoms of poisoning abate.

Dusting powders including the insoluble salts of bismuth, starch, boric acid, zinc oxid and zinc stearate are used to protect inflamed skin, and collodion and oiled silk are used to exclude the air from inflamed surfaces. Flexible collodion affords an impervious covering which may be used on cuts and small non-infected wounds.

Lime liniment is specially used in the treatment of burns, promptly relieving the pain, but it has the great disadvantage of being uncleanly and difficult to remove and of permitting the development of bacteria beneath it.

MATERIA MEDICA

Acacia.—Acacia, U. S. P., commonly known as gum arabic, is soluble in water but practically insoluble in alcohol. It is frequently used in the form of:

Mucilago Acaciae.—Mucilage of Acacia, U. S. P., containing about 34 per cent. of acacia.

Tragacantha.—Tragacanth, U. S. P., swells on addition of water and gradually forms a cloudy gelatinous mass or viscid mucilage.

Linum.—Linseed, Flaxseed, U. S. P., unground, forms a thin mucilage with water. When ground and mixed with from two to three times its weight of boiling water it yields a rather firm mass much used as a poultice.

Amylum.—Starch, Corn Starch, U. S. P., occurs in the form of a fine white powder or as irregular friable white masses. It is insoluble in water or alcohol, but when boiled with water it yields a gelatinous mixture which, depending on the amount of water present, may be used as a cataplasm, a paste or a mucilage. Starch

itself is widely used as a dusting powder and as a diluent for active substances.

Among the fats, bland oils and related substances that are used as emollients are:

Adeps.—Lard, U. S. P.

Adeps Benzoïnatus.—Benzoinated Lard, U. S. P.

Adeps Lanae Hydrosus—Hydrated Wool Fat, U. S. P., better known as lanolin, a mixture of 3 parts of water with 7 parts of wool fat.

Petrolatum.—Petrolatum, U. S. P.

Petrolatum Liquidum.—Liquid Petrolatum, U. S. P.

Glycerinum.—Glycerin, Glycerol, U. S. P., occurs as a clear colorless liquid of syrupy consistence miscible in all proportions with water or alcohol.

Among the drugs that are used as dusting powders are:

Acidum Boricum.—Boric Acid, U. S. P.

Bismuthi Subcarbonas.—Bismuth Subcarbonate, U. S. P.

Bismuthi Subgallas.—Bismuth Subgallate, U. S. P., also known as "Dermatol."

Bismuthi Subnitrates.—Bismuth Subnitrate, U. S. P.

Bismuthi Subsalicylas.—Bismuth Subsalicylate, U. S. P.

Zinci Stearas.—Zinc Stearate, U. S. P.

Zinci Oxidum.—Zinc Oxid, U. S. P.

The latter two substances are frequently used in the form of ointments. One of them is official as:

Unguentum Zinci Oxidi.—Ointment of Zinc Oxid, U. S. P., a mixture of zinc oxid 20, with benzoïnated lard 80 parts.

ASTRINGENTS

Astringents precipitate proteins and cause shrinking of mucous membranes. When applied to inflamed surfaces they cause diminished permeability of the smaller superficial vessels and allay pain due to sensory irritation. They lessen the secretory activity of the gastro-intestinal and other mucous glands, this action being of some importance when the astringents are used in the treatment of diarrhea.

The vegetable astringents act mainly by means of tannins, a group of ill-defined substances characterized by an astringent action and the property of forming black precipitates with ferric salts.

The official tannic acid is soluble in the gastric juice, and in solution combines with the proteins present in the stomach or attacks the gastric mucous membrane. The tannin of gambir (gambir replaces catechu of the pharmacopeia of 1890), however, is protected by the presence of gum and extractives. When gambir is administered it passes into the intestine, on which it exerts its astringent action, lessens the intestinal secretion and modifies the conditions under which bacteria develop during the inflammation of the mucous membrane.

Certain of the metallic albuminates, such as that of mercury, are soluble in the tissue fluids and by means of its corrosive action the metal destroys cells with which it comes in contact, this action being especially pronounced with mercuric chlorid and zinc chlorid. Albuminate of lead is insoluble in the tissue fluids and when the lead salts are applied in suitable concentration they form an impervious protective coating to the inflamed surface.

The actions of astringents, irritants and caustics differ largely in degree, many of the caustics being astringent when applied in sufficiently dilute solution, and the astringents causing irritation when they are used in too great concentration.

PICRIC ACID

Picric acid has recently attained some prominence as an external application in the treatment of various inflammatory conditions of the skin, but it is not a new remedy, crystalline picric acid having been prepared more than a century ago. It was used internally and externally with little discrimination, and fell into disrepute owing to the dangers that attended its use.

It has been included in "Useful Drugs" because of its value as an external application, more particularly in the treatment of burns, and this recognition should

not be understood as an endorsement of the claims that have been or are being made for it in all sorts of diseases.

Overdoses cause irritation of the gastro-intestinal tract with nausea, vomiting and diarrhea. When absorption occurs, there is a characteristic staining of the skin and mucous membranes which may simulate jaundice, but differs from it in that there is no bile in the urine. This staining of the skin and mucous membranes is due to the extraordinary affinity of the acid for epithelium. Its presence in the skin gives rise to itching and sometimes to erythema.

It destroys red blood cells when it is administered to animals in large doses, but it is said that this has not been observed in cases of poisoning in man. The irritant action on the kidneys induces nephritis. Fatal doses cause convulsions and collapse, with death by paralysis of the respiratory center.

It is excreted by the kidneys in the form of picramic acid ($C_6H_2OHNH_2(NO_2)_2$), which is closely related chemically to picric acid. The urine is colored yellow or reddish.

Like phenol, it is antiseptic and anesthetic, and on these and its astringent actions (in dilute solution) its value as an external application depends. Concentrated solutions are irritant.

THERAPEUTIC USES

The astringents are not used in the treatment of the diarrhea of infants nearly so much as formerly, the complaint being now treated mainly by diuretic measures.

Tannin as such, or in one of the preparations of gambir (catechu), kino or krameria, is sometimes used internally in the treatment of diarrhea; but owing to its tendency to cause nausea and vomiting, especially when given in too great concentration, one of the combinations of tannin with protein, such as tannalbin, is commonly preferred.

Tannin is used in the form of a gargle or troches in relaxed conditions of sore throat. A solution is sometimes used to harden the skin over bony protuberances to prevent bed-sores.

Tannin is sometimes used in the form of an ointment (20 per cent.) or of suppositories, each containing 0.3 gm. (5 grains) for the relief of painful bleeding internal piles, and for prolapse of the rectum. It is irrational to employ opium locally in this way, despite the fact that the well-known galls and opium ointment does afford relief, since the ointment of tannin alone is equally efficacious.

Tannin is frequently directed to be used as a precipitant in poisoning with alkaloids, but the official tannin is not usually readily available in the household and tannin-bearing household articles, such as tea and coffee, are not dependable for this purpose.

Tannin is widely distributed in the vegetable kingdom and many pharmaceutic preparations of vegetable drugs have a wide range of incompatibilities. It is therefore better to avoid prescribing ferric salts and alkaloids especially, with such preparations.

The systemic actions of iron, lead and other metals have been discussed, but their uses as astringents and styptics remain to be considered, lead being employed therapeutically only for its astringent action.

Lead acetate is sometimes used with opium in the treatment of diarrhea, but its use should not be long continued lest chronic poisoning be induced. A dilute solution of lead subacetate is used in inflammations and for sprains and bruises, but it should not be applied to the broken skin.

The well-known lead and opium wash is popular as a local application, but the alkaloids of opium are not absorbed to any appreciable extent under these conditions and they have no local analgesic action. A compress wet with lead water will probably answer any purpose that the lead and opium wash serves, and it is more cleanly.

Alum is seldom used internally, though a solution containing from 1 to 5 per cent. is sometimes used as a gargle, but the teeth should be protected against its injurious action. Exsiccated alum is actively astringent and even caustic; it is applied to cankers in the mouth and to chronic ulcers.

Aluminum acetate solution is widely used as an astringent application to infected wounds.

The irritant action of copper sulphate and zinc sulphate explains the use of those salts as emetics. Dilute solutions of zinc acetate and sulphate are used as astringent applications in the urethra, in the eye and in the vagina.

The chlorid of zinc is corrosive; the oxid and stearate are mild astringents and are used as dusting powders on ulcers and inflamed surfaces of the skin.

The tincture of ferric chlorid is commonly used in gargles for sore throat, especially in combination with potassium chlorate. It has been suggested that the alcohol in the tincture be evaporated and replaced with water, the resultant mixture to be used on tampons for checking uterine hemorrhage. The tincture of ferric chlorid or the solution of the subsulphate is sometimes added to glycerin and painted on the throat.

A hot saturated solution of potassium chlorate has often been used as a gargle and mouth wash. Tincture of myrrh is sometimes added to mouth washes and gargles.

In recent years potassium chlorate has been used as the active constituent of tooth pastes and powders. The assumption is that in contact with putrefying organic matter the salt liberates nascent oxygen and thus acts as an antiseptic as well as an astringent. This theory is highly improbable.

Bismuth subcarbonate, subgallate and subnitrate are commonly discussed among the astringents. Their use, however, in the treatment of diarrhea seems to depend on their capacity for forming a mechanical protective covering for the intestinal mucous membrane rather than on any slight astringent action that they may exert. Bastedo states that they act in a purely mechanical manner as a protective and demulcent to the mucous membrane of the stomach and intestine.

More than twenty-five years ago Harnack called attention to the neglect of certain well-known drugs by clinicians and attempted to explain the therapeutic actions of lime water in the treatment of diarrhea and

as a solvent for diphtheritic false membrane. It is unfortunate that more pharmacologists and clinicians do not devote their energies to the investigation of some of the simple remedies of proved value, but which we understand all too little.

Lime water is useful in the treatment of infantile diarrhea because of its astringent effect, and in some cases, because it neutralizes the acid secretions attending the condition. The insoluble calcium salts formed serve to close the finer openings through which bacteria would penetrate. They lessen excretion in the same way, and further, they form a protective covering for the mucous membrane.

The calcium soaps formed with the higher fatty acids are insoluble and have a caoutchouc-like consistency. It has been suggested that their action on the cell lipoids and intercellular substance is a toughening one. Calcium salts are supposed to lessen the permeability of the smaller blood vessels even in those parts of the body that they reach only through the circulation. This systemic action may be induced and the intestinal catarrh controlled when lime water is taken by the mouth, though this action must be rather slight, for, as already stated, most of the calcium is converted into insoluble salts in the intestine—but not in the acid secretions of diarrhea.

Harnack emphatically praises lime water in the treatment of diphtheritic sore throat, in which it dissolves the mucin in the false membrane, permitting the fibrin to fall apart, after which the lime water acts as an astringent. Lime water is sufficiently alkaline to be irritant to a sore throat.

Ichthyol penetrates the unbroken skin to some extent and constricts the superficial blood vessels, hence it is used to lessen hyperemia in a variety of inflammatory conditions of the skin including erysipelas, and acne vulgaris. Grossly exaggerated therapeutic claims have been made concerning its use in a wide variety of conditions, but it has not gained greatly in favor during the past few years.

Drugs containing tannin are no longer used to the extent to which they were at one time and it is now

generally recognized that tannic acid or one of the albumin compounds of this substance will answer practically all indications for a vegetable astringent.

Picric acid is commonly used in the form of a solution composed of 1 part of picric acid, 10 parts of alcohol and 150 parts of water. Cloth or gauze is wetted with this solution and applied to the part affected several times a day, or small areas of the skin may be kept wet with it if care is exercised to see that absorption does not occur.

This solution is said to be especially useful in the treatment of burns, in which case it is advised that the injured area be cleansed, and a cloth saturated with this solution be applied. A pad of absorbent cotton is fastened over the cloth by means of a light bandage. The dressing dries rapidly, and may be left undisturbed for several days. It is painful in some cases. It should not be applied to large surfaces because of the danger of absorption.

H. B. Wilcox states that in acute eczema with profuse exudation, excoriation, and formation of crusts, the application of solution of picric acid caused almost immediate lessening of the itching and pain with a reduction of the serous exudate. It was less useful in the subacute and chronic types. He states that the danger of absorption is negligible, though he applied the solution several times a day and allowed it to dry in mild cases, but applied wet dressings of the acid held in place by a facial mask in the more severe ones.

According to Sollmann* it is useful in the treatment of "bakers' eczema."

Picric acid solution is also used in various conditions of the skin, such as intertrigo, herpes labialis, erysipelas, ringworm, and for fissured nipples.

A saturated solution (about 1.5 per cent.) has been applied to the eruptions in pellagra, and a weaker solution (1:200) has been used as a gargle in that disease.

The intense staining of the clothing and skin constitutes a serious annoyance when picric acid is used.

* Personal communication to the authors.

Its poisonous nature must be remembered, and care should be taken to avoid absorption, even when it is applied to the skin.

MATERIA MEDICA

The astringents most widely used are:

Acidum Tannicum.—Tannic Acid, U. S. P., tannin, occurs as a light yellowish powder very soluble in alcohol, water and glycerin.

Glyceritum Acidi Tannici. — Glycerite of Tannic Acid, U. S. P., is a 20 per cent. solution of tannic acid in glycerin.

Typical of the albumin compounds of tannic acid that are receiving recognition at the present time is:

Tannalbin.—Tannalbin, N. N. R., tannin albuminate, insoluble in the gastric juice and becoming effective only when it reaches the intestine.

Plumbi Acetas.—Lead Acetate, U. S. P., popularly known as sugar of lead, occurs as crystalline masses or a heavy white powder, freely soluble (1:2) in water and soluble (1:30) in alcohol.

For external use the preparation usually preferred is the following:

Liquor Plumbii Subacetatis.—Solution of Lead Subacetate, U. S. P., an aqueous solution containing not less than 25 per cent. of lead subacetate. As a wash it is usually diluted with from 15 to 30 times its bulk of water.

Other mineral astringents that are used for various purposes are:

Alumen.—Alum, U. S. P., a crystalline product containing 12 molecules of water.

Alumen Exsiccatum.—Exsiccated Alum, U. S. P., the anhydrous product which occurs in the form of a white granular powder.

Alumini Acetas.—Used principally in the form of:

Liquor Alumini Acetatis.—Solution of Aluminum Acetate, N. F., a clear, colorless solution containing about 8 per cent. of basic aluminum acetate.

Cupri Sulphas.—Copper Sulphate, U. S. P., popularly known as blue vitriol, occurs in crystalline form, is soluble (1:22) in water but only slightly soluble (1:400) in alcohol.

Zinci Sulphas.—Zinc Sulphate, U. S. P., occurs in small crystals or as a granular powder, is very soluble (1:0.53) in water, but practically insoluble in alcohol.

Zinci Acetas.—Zinc Acetate, U. S. P., occurs as soft pearly crystals, is freely soluble (1:2.5) in water and soluble (1:36) in alcohol.

Zinci Chloridum.—Zinc Chlorid, U. S. P., when properly kept, occurs as a white granular powder, is very soluble (1:0.5) in water and in alcohol.

Ferri Chloridum.—Ferric Chlorid, U. S. P., has been used in medicine in the solid form and as an aqueous solution, but principally in the form of:

Tinctura Ferri Chloridi.—Tincture of Ferric Chlorid, U. S. P., a hydro-alcoholic solution containing not less than 13.28 per cent. of the anhydrous salt representing about 4.5 per cent. of metallic iron.

Potassii Chloras.—Potassium Chlorate, U. S. P., occurs as crystals or as a white granular powder. It is soluble (1:16) in water but nearly insoluble in alcohol. Potassium chlorate forms an explosive mixture with oxidizable material, and due caution must be observed in manipulating it.

Ichthyol.—Ichthyol, N. N. R., an aqueous solution of ammonium sulpho-ichthyolate, occurs as a reddish brown or brownish black syrupy liquid that is miscible with water but is incompletely soluble in alcohol.

Acidum Picricum. — Picric Acid ($C_6H_2.OH(NO_2)_3$) N. N. R., an acid obtained by nitrating phenol, occurs as yellow crystalline needles or scales having an acid reaction, a bitter taste and imparting an intense yellow color to aqueous solutions. It is soluble (1:81) in water and freely soluble (1:10) in alcohol. Picric acid forms insoluble compounds with many alkaloids and precipitates albumin in the cold.

RUBEFACIENTS

Inflammation is a local reaction to irritation that tends to limit the area of injury, to remove the injurious substance and the tissues that may be destroyed, and to repair the damage. There is increased permeability of the smaller vessels with the other well-known symptoms of inflammation including redness, heat, swelling and tenderness or pain.

While inflammation is sometimes a useful process it may be present when it is not useful or it may exceed the limits of usefulness.

Evidence is abundant that inflammation results from the irritation of sensory nerves, but the precise mechanism by which this is brought about is not understood. In therapeutic practice irritants of various types are used to induce different stages of inflammation, most frequently that of redness only, and the agent so used is termed a rubefacient. If a somewhat more intense action is elicited, a blister is formed by the collection of the transudate under the horny layer of the skin. This is termed vesication. Pus formation is rarely induced intentionally at present, but pustulants were formerly used to some extent. Caustics destroy the tissue to which they are applied, hence they are used mainly for the removal of callus and for application to small areas when it is desired to remove exuberant growth.

Rubefacients are applied to the skin for the purpose of causing an increased blood supply to relieve organs in which congestion due to diminished circulation has caused inflammation to reach the stage of pain. Since this is accomplished through causing irritation at the seat of application such agents are called counter-irritants.

Ross, Mackenzie, and more especially Head, have put the use of rubefacients on a rational basis. Ross observed the location of painful cutaneous areas complained of by patients who suffered with visceral disease and he suggested that pain was referred along the distribution of somatic nerves which came off from the same part of the cord as the sensory sym-

pathetic fibers to the organs affected. Head was stimulated (to use his own expression) by Ross' suggestion to make careful observations of the areas of cutaneous tenderness in sixty-two cases of herpes zoster, and was surprised to find that these areas correspond exactly with those with which he was familiar in visceral disease. Head mapped out the cutaneous surface of the body and limbs, dividing it into areas each of which corresponds to the distribution of nerve fibers given off from a segment of the spinal cord.

He suggested that the skin is tender in visceral disease because impulses (not painful) pass up the sensory nerves from the diseased organ and set up a disturbance in the segment of the cord to which they are conducted. When a secondary impulse from the skin is conducted to that disturbed segment of the cord the impulse will be altered and exaggerated, so that a stimulus that would not be painful under ordinary circumstances now becomes so, for example, the application of slight warmth then causes a burning sensation.

When there is congestion of an internal organ the application of a rubefacient or more active irritant to the corresponding area of the skin causes vasodilatation in the viscus with relief of the congestion and the attending pain. We do not know the exact mechanism by which this is accomplished, but we do know that the application of rubefacients does often relieve pain and congestion in internal organs in this way.

Head suggests that the head of a common pin—not the point—be used in eliciting tenderness in the skin, or that this may be done by pinching the skin gently between the thumb and forefinger.

The number of irritants is very large and the choice is often determined by convenience of application, care being taken to limit the action of the more active members of the group when they are used.

Among the rubefacients most commonly used are: Alcohol, ammonia, camphor, chloroform (causes blistering readily), capsicum, iodine, menthol, mustard

and oil of turpentine. Croton oil is sometimes used as a rubefacient but it tends to produce pustulation. Heat in its various forms is probably the most commonly used of the rubefacients.

The various therapeutic applications of the rubefacients cannot be discussed in this place, but an understanding of the principles involved is necessary for their rational use. Nearly all textbooks of therapeutics and pharmacology give the cutaneous areas corresponding to the internal organs as determined by Head.

MATERIA MEDICA

Rubefacients are used principally in the form of liniments or solutions for external application. Among the widely used official liniments are:

Linimentum Ammoniae.—Ammonia Liniment, U. S. P.

A mixture of ammonia water (35), alcohol (5), and a fatty oil (60).

Linimentum Camphorae. — Camphor Liniment, U. S. P.

Camphorated Oil, a solution of Camphor (20) in cottonseed oil (to make 100).

Linimentum Saponis.—Soap Liniment, U. S. P.

A solution of soap, camphor and oil of rosemary in a mixture of alcohol and water.

Soap liniment is used quite extensively as a vehicle for active rubefacients, such as chloroform, oil of turpentine, oil of mustard, tincture of capsicum, menthol, ammonia, or croton oil, all of which it dissolves more or less readily. A type of this form of preparation is found in the official:

Linimentum Chloroformi.—Chloroform Liniment, U. S. P.

A mixture of chloroform (30) with soap liniment (70).

The solutions used for external application are chiefly alcoholic solutions of the rubefacients mentioned above. A type of these solutions is the official.

Tinctura Iodi.—Tincture of Iodin, U. S. P.

An alcoholic solution, each 100 c.c. of which contains 7 gm. of iodine and 5 gm. of potassium iodide.

VESICANTS

When it is desired to carry irritation to the stage of vesication cantharides or cantharidin is commonly used. The action develops slowly, eight hours being frequently required before vesication is induced. When cantharides is employed for a short time it acts as a rubefacient, but in such cases it has no apparent advantage over the more rapidly acting members of the group, such as mustard.

Cantharidin, the active principle of cantharides, is excreted by the kidneys after its absorption into the circulation and gives rise to irritation of the genito-urinary tract—a circumstance that has led to its abuse in some instances.

Cantharides is sometimes added to liniments and to hair tonics, and while it may enhance the rubefacient action of these it probably has no specific action on the scalp or hair follicles, and is therefore probably useless as a hair restorative.

MATERIA MEDICA

The more important vesicants are:

Cantharis.—Cantharides, U. S. P., which is frequently used in the form of:

Ceratum Cantharidis.—Cantharides Cerate, U. S. P. Usually applied as a plaster.

Sinapis Nigra.—Black Mustard, U. S. P.

Used in the form of a plaster or as:

Charta Sinapis.—Mustard, U. S. P., which consists of a layer of black mustard on well-sized paper.

Oleum Sinapis Volatile.—Volatile Oil of Mustard, U. S. P., obtained from black mustard by maceration with water and subsequent distillation; also made synthetically.

CAUSTICS OR CORROSIVES

Strong acids and alkalies and certain of the metallic salts destroy the tissues and dissolve them. Phenol in concentrated solution precipitates the proteins of cells and destroys them.

Acids, alkalies, phenol and certain other caustics are of some toxicologic interest because of the frequency with which they are swallowed accidentally. In such cases the gastro-intestinal injury may result in shock or in perforation with peritonitis. The corrosive action in the mouth and throat may be followed by cicatricial contraction, and esophageal stricture has frequently resulted from swallowing concentrated alkalies and acids and perhaps from phenol.

The stomach should be washed as promptly as possible after a corrosive has been swallowed, using a large amount of water and the appropriate antagonist in dilute form. Thus, if a mineral acid has been swallowed, a weak alkali such as magnesium oxid, lime water or weak soap solution, should be added to the water used to wash the stomach; if a caustic alkali has been swallowed then a weak acid, such as dilute vinegar, should be administered with the wash water. After the stomach has been washed, demulcents, including butter, cream, milk, white of egg or a bland oil, such as olive oil, should be administered. Bismuth subcarbonate suspended in water affords a useful protective covering for the mouth, throat and mucous membrane of the stomach in such cases.

It is generally held that sodium bicarbonate liberates too much gas to justify its use after a caustic acid has been swallowed, but it is commonly at hand in the household and it should be employed in an emergency if lime water, magnesia or pure castile soap is not available.

Strong nitric or glacial acetic acid is sometimes used for cauterizing sores and for the removal of warts. The surrounding tissue is coated with petrolatum and the acid applied to the wart with a stick or glass rod for a short time.

Corns are commonly treated with salicylic acid dissolved in collodion, which insures the continued caustic action of the acid. The coating is removed after having been applied for about twenty-four hours. The treatment is painful, however.

Lunar caustic, or molded silver nitrate is a convenient caustic for the destruction of exuberant granulating tissue.

Concentrated solutions of silver nitrate, even up to 50 per cent., are used in the treatment of sore throat and tonsillitis. The solution is painted on the throat or swollen tonsils and the throat is immediately gargled with salt solution in order to neutralize the excess of silver nitrate by converting it into the insoluble and harmless silver chlorid. This is said to be especially efficacious in severe forms of tonsillitis. Extreme care must be taken to insure that none of the solution is swallowed and that the excess of the caustic is neutralized immediately with sodium chlorid solution.

MATERIA MEDICA

Among the available caustics and corrosives are:

Argenti Nitras.—Silver Nitrate, U. S. P.

Lunar Caustic, occurs in colorless crystals which become gray or grayish black on exposure to light. Silver nitrate is very soluble (1:0.54) in water and soluble (1:24) in alcohol. It fuses when heated and this property is frequently utilized to form a coating of the caustic material on the end of a silver wire or probe. It is also used in making:

Argenti Nitras Fusus.—Moulded Silver Nitrate, U. S. P., occurs as a white hard solid containing a small proportion of silver chlorid for the purpose of toughening the mass.

Acidum Aceticum.—Acetic Acid, U. S. P.

The glacial acetic acid which contains not less than 99 per cent. by weight of absolute acid is sometimes used.

Acidum Nitricum.—Nitric Acid, U. S. P.

A liquid containing about 68 per cent. by weight of hydrogen nitrate, occurs as a colorless, fuming, caustic and corrosive liquid. Care should be exercised to control the corrosive action.

Potassii Hydroxidum. — Potassium Hydroxid, U. S. P., and

Sodii Hydroxidum.—Sodium Hydroxid, U. S. P., are sometimes used as caustics for the removal of warts, corns and other excrescences, but their corrosive action is not readily controlled.

CHAPTER XIII.—MISCELLANEOUS SALTS, ACIDS AND ALKALIES

MISCELLANEOUS SALTS

The systemic actions of a soluble salt are determined, as a rule, either by the anion alone or by the cation, but both ions are concerned in the actions of some salts.

Sodium and potassium are of physiologic importance but we know little of their actions that would indicate that one should be used therapeutically rather than the other in any given condition. It is often stated, however, that certain important differences are observed between the actions of sodium bromid and those of potassium bromid.

The rapid injection of large amounts of potassium salts directly into the circulation induces cardiac paralysis, but this action is not observed when the potassium salts are used therapeutically. It is sometimes maintained that the salts of ammonium or sodium should be used when cardiac depression from the action of potassium salts is to be feared.

Lithium is of neither therapeutic nor physiologic importance, but has become popular to a certain degree because of the erroneous belief that it is capable of dissolving uric acid calculi in the bladder. This misconception arises from the fact that salts of lithium do promote the solubility of uric acid and urates when tested under conditions that can never obtain in the bladder.

None of the salts of lithium are of sufficient importance to merit inclusion in the Council's list of "Useful Drugs."

The erroneous belief concerning the efficiency of lithium salts as solvents for uric acid has led to conditions that would be ludicrous were they not of a nature so little to our credit as physicians. Numerous

proprietary preparations of lithium salts have been exploited widely as uric acid solvents and this action has been urged as the basis for their use in innumerable conditions in which it is claimed that uric acid plays an important rôle. The absurdity has reached its climax in the exploitation of so-called lithia waters. It has been shown that about two hundred thousand gallons of Buffalo Lithia Springs water contains an amount of lithium equal to only one therapeutic dose.

The rapid intravenous injection of large doses of ammonium salts causes strychnin-like convulsions, but these effects are never seen when those salts are administered by the mouth because they are decomposed in the body or eliminated almost as rapidly as they are absorbed. Hence after their oral administration their concentration in the blood never reaches the degree required to cause convulsions or hyperexcitability.

A fleeting stimulation of the central nervous system by ammonium is attained in the use of smelling salts in the treatment of fainting. Ammonium carbonate is frequently used to stimulate the respiratory center when this is depressed and when there is mechanical interference with respiration, as in asthma and especially in pneumonia. The use of ammonium acetate as a diaphoretic has been mentioned, the effect being attributed to its action on the central nervous system. The use of ammonium chlorid in the treatment of sore throat and cough has been mentioned in connection with other expectorants.

Calcium is an important element in the body, small amounts being found in the blood in which it is essential for the beat of the heart, and much larger amounts are found in the bones.

The normal diet probably contains more calcium than the body requires, but when calcium is withheld from the food of growing animals symptoms resembling those seen in rickets and osteomalacia are induced. This has led to the administration of calcium in the treatment of those conditions. It appears, however, that these conditions arise from an inability to utilize calcium, rather than from a deficiency of it in the food in most cases, hence calcium used therapeu-

tically frequently fails to cause improvement. Emerich and Lowe believe that the daily food is often deficient in calcium and they recommend the routine use of as much as 1.5 gm. (22 grains) of calcium chlorid daily in health, and as much as 10 gm. ($2\frac{1}{2}$ drams) daily in disease. It is difficult to believe that such amounts are often indicated.

A diminution of calcium below normal in the circulation causes nervous irritability.

Such a depression of the central nervous system as is sometimes observed when magnesium salts are used subcutaneously in very large doses, as in the treatment of tetanus, can be relieved at once by the subcutaneous or intravenous injection of calcium chlorid.

Doses of from 0.30 to 0.40 gm. of calcium chlorid per kilogram of body-weight, corresponding to from 300 to 400 grains for a man, injected subcutaneously, gradually produce a fatal result in animals.

The intravenous injection of calcium salts into animals reduces their susceptibility to local irritants such as mustard, probably because of a lessened permeability of the smaller blood vessels. While normal dogs are resistant to the experimental induction of moist eczema their resistance is reduced by the injection of oxalates which precipitate the calcium in the circulation. It has thus been suggested that calcium salts should be used therapeutically in the treatment of moist eczema in man. It is also used on the same basis in the treatment of urticaria and to prevent serum rashes.

When administered by the mouth, a part of the salts of calcium are absorbed, but the larger portion is converted into insoluble phosphate or carbonate and excreted in the feces, the part that is absorbed being usually insufficient to exert any marked systemic effect.

The salts of calcium are administered to prevent or control hemorrhage during typhoid fever, and in hemophilia because of their supposed power to increase the coagulability of the blood.

Calcium chlorid will usually suffice for the administration of calcium, though there is no particular reason why one of the other salts should not be used if preferred for any reason. Calcium lactate has been rec-

ommended by many because of its being less irritant than the chlorid and therefore preferable for subcutaneous injection. Calcium hypophosphite is wholly superfluous and its use should be discouraged as it tends to perpetuate a mistaken idea of the value of the hypophosphites in general.

DOSAGE

The average dose of calcium chlorid is 0.5 gm. ($7\frac{1}{2}$ grains). If larger doses are required to abolish the paralytic action of magnesium salts when such action is induced accidentally, small doses should be given subcutaneously and repeated if necessary, or a dilute solution (1:200) may be slowly injected intravenously until improvement occurs or until the full therapeutic dose has been administered. Concentrated solutions must not be injected subcutaneously as they cause abscesses. Calcium lactate may be given in doses of from 0.5 to 2 gm. ($7\frac{1}{2}$ to 30 grains).

Lime water, a solution of calcium hydroxid, is an antacid and has been used as a solvent for the false membrane of diphtheria, but it is not used to produce the systemic action of calcium.

Attempts have been made at various times to popularize the salts of strontium but these have no advantage over the corresponding salts of the alkalies and none of the strontium salts has been admitted to "Useful Drugs."

MATERIA MEDICA

The soluble salts of calcium in popular use are:

Calcii Chloridum.—Calcium Chlorid, U. S. P.

It occurs as white translucent fragments having a sharp saline taste. It is very deliquescent, is freely soluble (1:1.3) in water and also (1:8) in alcohol. The unpleasant acrid taste of calcium chlorid is difficult to mask and it is best administered in dilute solution flavored with syrup of citric acid or the official elixir of orange.

Calcii Lactas.—Calcium Lactate, N. N. R.

It occurs in white crystalline masses or a comparatively fine powder, odorless and tasteless. It is soluble (1:15) in water but only slightly soluble in alco-

hol. The large doses of calcium lactate frequently given may be directed to be suspended in water, or the substance may be dispensed in powder or in cachets.

The soluble salts of calcium are incompatible with carbonates, phosphates, tartrates and sulphates and are preferably dispensed in simple solution.

THE BROMIDS

Animal experiments have failed to throw much light on the actions of the bromids on the central nervous system because of the comparatively slight action on the centers in animals unless doses are used that cause other toxic actions.

The bromids of the alkalies are irritant to the stomach and sometimes cause nausea and vomiting, especially when they are given in concentrated solutions or in the form of tablets. Tablets are convenient for dispensing but they should be dissolved in at least fifty times their weight of water before being taken.

The bromids cause mental depression with dulness and confusion of ideas, hence they are not so useful as hydrated chloral in simple wakefulness unattended with pain or nervous irritability, but they are useful in combination with hydrated chloral when these symptoms are present.

The bromids depress the centers in such a way that reflexes are diminished, while impulses passing from the brain to the periphery are said to be unaffected. They are therefore effective in controlling the reflex excitability of strychnin and may abolish the convulsions unless the dose of the strychnin has been excessive.

Large or frequently repeated doses of the bromids often give rise to a condition known as bromism, the readiness with which such symptoms develop in different individuals being subject to wide variation.

The symptoms of bromism include various skin eruptions, acne of the face being very common, and digestive disturbances which are sometimes attributed to the hydrobromic acid that is excreted into the stomach, but which are probably due largely to the local irritant action of the salt. The memory suffers

severely and the other mental disturbances already mentioned are exaggerated. Muscular tremors also occur. The symptoms usually disappear if the drug is discontinued, but the patient is said to be more susceptible than normally to certain infectious diseases while suffering from bromism.

The bromids depress the respiratory center, and the sexual appetite is diminished or abolished.

The bromids are absorbed readily from the gastrointestinal tract and they may be detected in the urine within a few minutes after their administration. The larger part of the drug, however, is fixed in the tissues, apparently displacing as much as one fourth of the chlorids of the blood when saturation is said to have taken place, and the elimination thenceforth keeps pace with absorption. The bromid that displaces the chlorids in combination with protein is eliminated slowly, so that some weeks may elapse after the administration is discontinued before the last of the bromid is eliminated. Other tissues beside the blood also show the replacement of chlorids by bromids. Saturation with the bromids is reached more rapidly if chlorids are withheld while the bromids are being administered and, as saturation is desired when the bromids are used in the treatment of epilepsy, it is customary to limit the chlorid ingestion at such times. Saturation with bromids is indicated by the appearance of hydrobromic acid in the stomach, and probably by the elimination of a larger amount in the urine.

The mutual displacement of chlorids and bromids indicates the treatment of bromid poisoning by chlorids. It has been suggested that the toxic symptoms of the bromids may be due, at least in part, to the absence of the chlorids that are displaced, rather than to any direct action of the bromids themselves.

The bromids are found in nearly all of the body fluids and excretions, and bromism may be induced in a nursing infant whose mother is taking bromids.

THERAPEUTIC USES

The bromids are used as hypnotics when sleeplessness results from nervous irritability; they are frequently used with hydrated chloral, in which case their

depression of the reflexes probably enhances the hypnotic action of the chloral.

They are especially useful in the treatment of epilepsy, in which they greatly diminish the number of seizures, or these may be abolished during the period that saturation with bromids is maintained. The attacks usually recur when the administration of the bromids is stopped.

The bromids are sometimes used for several days before operations on the throat and before examination with the mirror for adenoids.

They are also used to quiet nervous excitability in neurasthenia and in hysteria.

A more or less widespread belief exists that a mixture of bromids is preferable to any one of them, and the widely known epilepsy mixture of Brown-Séquard contained the bromids of sodium, potassium and ammonium together with some others. There is no evidence that such mixtures have any advantage over potassium bromid alone.

Certain organic compounds of bromin have been introduced as hypnotics, but there is no satisfactory evidence that these are better than the inorganic.

DOSAGE

The average dose of sodium or potassium bromid is usually given as 1 gm. (15 grains), but 0.3 to 0.6 gm. (5 to 10 grains) is the dose commonly used as a hypnotic with hydrated chloral. In the treatment of epilepsy it is advisable to begin with doses of 1 gm. (15 grains) and increase until as much as 10 gm. (2½ drams) are taken daily, until saturation is attained or until symptoms of bromism indicate the limits of tolerance.

The bromids are sometimes given in doses varying from 0.3 to 0.6 gm. (5 to 10 grains), dependent on the age of the child, three times daily for a week, in order to lessen the sensitiveness of the nasopharynx in preparation for mirror examination for suspected adenoids.

MATERIA MEDICA

The more widely used bromids are:

Potassii Bromidum.—Potassium Bromid, U. S. P.

It occurs as colorless crystals or a granular powder having a strongly saline taste. It is freely soluble (1:1.5) in water but only slightly soluble (1:180) in alcohol.

Sodii Bromidum.—Sodium Bromid, U. S. P.

It has the general physical characteristics of potassium bromid, but is more hygroscopic. It absorbs moisture from the air without deliquescing. It is freely soluble (1:1.7) in water and soluble (1:12.5) in alcohol. The solution is devoid of the bitter taste of potassium bromid.

The alkali bromids are preferably given in aqueous solutions, with or without syrup. The ready made preparations such as the elixirs of bromids, usually contain considerable quantities of alcohol and are objectionable for this reason.

The bromids of the alkalies are incompatible with mineral acids, the salts of mercury, spirit of nitrous ether and oxidizing substances generally.

IODIDS

Our knowledge of the pharmacologic actions of the iodids does not permit of a systematic discussion of them as a basis for their therapeutic uses.

The systemic effects frequently observed after the administration of the iodids are commonly described under the term iodism, and these are often seen after small doses as well as after larger ones. It is even asserted that when they appear after small doses they may disappear if the dose is increased. This may be true but it has not been demonstrated satisfactorily that the disappearance in such cases is due to the increase in dosage.

Catarrh of the respiratory passages is probably the commonest of the symptoms of iodism. There is often swelling of the larynx with edema that interferes with respiration, occasionally necessitating tracheotomy, and rarely causing death. Bronchitis is not infrequent, and the eyes are commonly suffused.

The respiratory symptoms are sometimes attributed to the liberation of free iodine by minute amounts of nitrites in the saliva and by carbon dioxide. It seems improbable that enough iodine could be liberated in this

way to give rise to the symptoms, for the larger part of a dose of iodid leaves the circulation promptly and the amount that can be detected in any of the tissues except the blood is extremely small.

Skin eruptions of the most various character occur more frequently after the drug has been administered for some time; these include erythematous patches, papular eruptions that may become pustular, eczema, bullae, pemphigus, purpura and many others. It is said that frequent bathing with scrupulous regard for the cleanliness of the skin lessens the severity of the skin manifestations.

The iodids of sodium and potassium are absorbed promptly from the gastro-intestinal tract. The larger portion is excreted rapidly in the urine unchanged, a portion remaining fixed in the tissues for some time, much as in the case of the bromids.

The excretion of the iodids in the urine begins within a few minutes, reaches its maximum in about two hours, and within twelve hours the greater part of a small dose is eliminated, but several days may be required for the practically complete elimination of a large dose. The elimination may be hastened by the administration of chlorids but not by simple diuretics, such as caffein. Small amounts of the iodids appear in the saliva and other secretions.

THERAPEUTIC USES

The iodids are used in combination with mercury in the treatment of the second stage of syphilis, and alone, or in combination with mercury in the third stage. Various explanations have been offered to account for the improvement that they induce, but no adequate explanation has been given of the truly remarkable effects that often follow their use in the treatment of syphilitic manifestations affecting internal organs. Other obscure manifestations of syphilis, such as neuralgia and disturbances of the central nervous system, often yield readily to iodid treatment.

They are extensively used in the treatment of chronic rheumatism, but the benefits they cause are unexplained. The effects of iodids on the thyroid, and

indirectly on conditions affected through the thyroid, will be mentioned when the thyroid is discussed.

The iodids are frequently used in arteriosclerosis partly perhaps because of their supposed capacity for lowering arterial tension, but there is no satisfactory evidence that they lower blood pressure appreciably. Their usefulness in this condition as in aneurysm is probably limited to their capacity for causing the absorption of syphilitic deposits in the walls of the vessels.

These salts have long been of special repute in the treatment of chronic poisoning by lead and mercury, and while some old experiments seem to show that they facilitate the elimination of lead, and possibly of mercury, the mechanism of the action is not known.

The iodids are sometimes used in the treatment of asthma. It has been suggested that they paralyze the vagus endings in the bronchi, thus relieving the spasm. While large doses of the iodids do depress the vagus endings, it is hardly conceivable that the small doses usually employed can have any such action. They are commonly used with belladonna or some other member of the atropin group, compared with which they can act only feebly on the vagus.

The iodids are contraindicated in tuberculosis, but they are used, nevertheless, in syphilis complicating tuberculosis. The increased susceptibility of the tuberculous to the iodids should be remembered when they are used in such conditions.

They have long been used in the treatment of actinomycosis and they are also of especial value in sporotrichosis and blastomycosis. In all of these they promote the absorption of granulomatous lesions.

Numerous organic compounds of iodine have been introduced for use in place of the alkaline iodids. Although these lack certain disadvantages of potassium iodid clinical experience shows that they are weaker than potassium iodid in the doses commonly used.

These compounds of iodine with proteins and with fats seem to irritate the stomach less than potassium iodid. It is asserted that they induce symptoms of iodism less readily, but these claims have not been sub-

stantiated in cases in which they are used in amounts sufficient to produce the full therapeutic effects.

Numerous compounds of iodine with protein and others with nonprotein substances are described in New and Nonofficial Remedies.

DOSAGE

Potassium iodid is used in nonsyphilitic conditions in doses of 0.3 to 2.0 gm. (5 to 30 grains) but much larger doses are employed to promote the absorption of the gummatous exudates in tertiary syphilis, in which 5 gm. (75 grains) and even larger amounts are used unless symptoms of iodism appear.

It may be prescribed in doses of 0.3 c.c. (5 minims) of a saturated solution administered three times a day after meals (at which time the stomach contents lessen the irritation) with a daily increase of 1 drop in each dose. While a saturated solution is convenient for measuring the dose it should be remembered that saturated, or even somewhat less concentrated solutions of salts are irritant to the stomach, hence these should be diluted with from half a glass to a glass of water before being taken. Bland fluids, such as milk, are better than water, and even with such dilution they should be taken only after food.

When symptoms of iodism occur the drug should be discontinued for a time and smaller doses used when the administration is resumed.

MATERIA MEDICA

The iodids in general use are:

Potassii Iodidum.—Potassium Iodid, U. S. P.

It occurs as colorless or opaque white cubic crystals or a granular powder having a pungent saline, afterward bitter taste. The salt is slightly deliquescent in moist air. It is very soluble (1:0.7) in water and soluble (1:12) in alcohol.

Sodii Iodidum.—Sodium Iodid, U. S. P.

It occurs as colorless crystals or white crystalline powder having a saline taste, practically devoid of bitterness. In moist air it deliquesces and frequently undergoes decomposition. It is very soluble (1:0.5) in water and freely soluble (1:3) in alcohol.

The alkali iodids like the bromids are incompatible with mineral acids, spirit of nitrous ether and oxidizing substances generally. They are also incompatible with bismuth salts and ferric salts, and should not be prescribed in solution with salts of alkaloids or with preparations of drugs having alkaloidal constituents.

The iodids are preferably prescribed in concentrated solutions that may be measured out in drop doses and directed to be taken well diluted with water or with such liquids as milk, or solutions of egg albumin. The following is a typical formula for securing a concentrated solution of an alkali iodid:

	gm.	or	c.c.	
R Potassii iodidi	25			1 ounce av.
Aquae destillatae.....q. s. ad	25			1 fl. ʒ

When larger doses of dilute solutions are used the disagreeable taste of the iodid may be masked by the addition of the compound syrup of sarsaparilla.

ACIDS

When an acid is taken into the mouth it acts reflexly to cause a flow of saliva, and it is partly neutralized thereby; the acid that passes into the stomach excites gastric secretion, and if in sufficient amount induces increased gastric movements. Free acid is fixed by proteins and is absorbed, or a part of it may pass into the duodenum, causing the production of secretin and promoting pancreatic and biliary secretion; but the latter actions are fleeting, and probably of no therapeutic importance.

If a moderate amount of free acid enters the duodenum, it is neutralized by alkali, the salt thus formed acts as a laxative or it undergoes absorption and causes diuresis if in sufficient amount. If a large amount of free acid enters the duodenum, it acts as an irritant and sets up peristalsis with diarrhea.

When mineral acid is taken internally, it diminishes the alkalinity of the tissues, causing the elimination of acid salts in the urine, but none of the free acid exists in the circulating blood, of course. With the elimination of the acid salts, the proportion of nitrogen that is eliminated in the form of ammonia is

larger than normally, and there is a corresponding decrease in the amount eliminated in the form of urea.

The acid salts lessen the solubility of the urates, and promote the solubility of the phosphates in the urine; but preformed phosphatic calculi are not brought into solution.

The diminished alkalinity of the blood is attended by dyspnea and other symptoms of acidosis. These symptoms may be relieved by the intravenous injection of a solution of sodium carbonate or by the rectal injection of a 3 per cent. solution of sodium bicarbonate in small amounts (250 c.c., 8 fluidounces) as frequently as possible without causing its expulsion, or by the slow continuous method.

Citric acid is oxidized in the body with the formation of carbonates.

A case is reported of a woman's having taken at least 12 gm. (3 drams) of tartaric acid in concentrated form. This was followed by severe pain, vomiting, diarrhea, and later by delirium, weak pulse, subnormal temperature, and death on the seventh day.

THERAPEUTIC USES

Citric acid is sometimes used in place of lemon juice in making lemonade, and citric and tartaric acids are used in making granular effervescent salts.

Acetic acid is seldom used internally, but it may be given well diluted with water, as a diaphoretic and diuretic. The only advantage that it has over potassium acetate when used in this way is that it has a less disagreeable taste.

Mention has been made elsewhere of the use of acid sodium phosphate (Na_2HPO_4) for increasing the acidity of the urine, especially when hexamethylenamin is used as a urinary antiseptic.

The corrosive and astringent actions of acids are discussed elsewhere.

MATERIA MEDICA

Acidum Aceticum.—Acetic Acid, U. S. P., a solution containing 36 per cent. by weight of absolute acetic acid ($\text{H.C}_2\text{H}_3\text{O}_2$). The diluted acetic acid of the pharmacopeia contains 6 per cent., and the glacial

acetic acid 99 per cent. by weight of absolute acetic acid.

Acidum Citricum.—Citric Acid, U. S. P., a tribasic organic acid, $\text{H}_3\text{C}_6\text{H}_5\text{O}_7$, H_2O . It forms transparent crystals having an agreeable acid taste. It is very soluble (1:0.54) in water, and freely soluble (1:1.5) in alcohol.

ALKALIES

The alkalies neutralize acids, dissolve mucus, combine with proteins to form soluble compounds, saponify fats, and alter the solvent powers of various fluids in which they are dissolved. Their effects on metabolism vary with conditions that are not understood.

Dilute solutions of the alkalies in contact with mucous membranes dissolve the superficial layers and concentrated solutions of the hydroxids, destroy the entire membrane within a few seconds, and deep corrosion of the mouth, throat, esophagus and stomach, with perforation of the latter may follow the swallowing of a solution of potassium or sodium hydroxid. When small amounts of these concentrated liquids have been swallowed, the corrosion is frequently followed by gastric ulcer and by cicatrices in the throat and esophagus that prevent swallowing.

If the amount of a dilute alkali taken is not excessive, it is neutralized in the stomach, and the chlorid formed is absorbed, the alkali causing no effect except that due to interference with gastric digestion and the temporary increase in the alkalinity of the blood and urine. Somewhat larger amounts pass into the duodenum and are absorbed, the character and intensity of the actions depending to a great extent on the concentration in which the alkalies are taken.

It was formerly taught that the administration of therapeutic doses of the alkalies causes increased gastric secretion, but they appear to have no important effect on the activity of the secretory apparatus. Obviously, if they are taken during digestion they will neutralize the acid in the stomach and interfere with peptic digestion, but if they are taken some time before eating they may serve to dissolve an excess of

mucus that may be present in the stomach, and thereby promote digestion without directly influencing the secretory activity of the stomach.

The effects of alkalies in the intestine are partly direct and partly indirect. The gastric juice destroys many bacteria, and when the acidity has been neutralized, many of these organisms escape destruction and they may multiply enormously in the intestine. In like manner the neutralization of the gastric juice interferes with the production of secretin, and thus indirectly with the pancreatic secretion; but with small amounts, or even with fairly large single therapeutic doses, this effect is slight.

The alkalies increase the alkalinity of the tissues even though they are completely neutralized in the gastric juice, since they spare a corresponding amount of carbonates in the intestine that would otherwise be used for neutralizing the chyme, and the carbonates so spared are absorbed. The normal degree of alkalinity of the blood and tissues is restored rapidly through the elimination in the urine of a larger proportion of dibasic phosphates than normally.

The increased alkalinity of the body fluids persists for periods varying with the amount of alkali taken and the rates of absorption and elimination. The urine is usually alkaline or only very slightly acid, for nearly twenty-four hours after one has taken a seidlitz powder, which contains sodium and potassium tartrate with molecular proportions of sodium bicarbonate and tartaric acid. This is of some importance when hexamethylenamin is being used as a urinary disinfectant.

There is an extensive literature dealing with the effects of alkalies on metabolism and secondarily on numerous diseases, much importance having been attached to the fact that the ammonia of the urine is often diminished during the administration of alkalies, while the urea is increased correspondingly. The alkalies do not appear to have any constant or important influence on the elimination of uric acid, which is sometimes increased and sometimes decreased by them.

There is a widespread belief that alkalies increase tissue waste, a belief that has been fostered by those interested in mineral waters, and several of the resorts where obesity is treated have gained wide celebrity. The effects obtained in such cases are due more to the laxative effects of the waters, to the diet imposed and the mode of life followed than to any direct effects of the alkalies on tissue waste.

THERAPEUTIC USES

The alkalies (usually the bicarbonates) relieve gastric hyperacidity and are given preferably about an hour after meals, but they are sometimes used an hour before meals when there is continuous secretion and for the purpose of dissolving mucus, as in alcoholic gastritis. A solution of potassium bicarbonate often affords almost instantaneous relief in sour stomach when there is an accumulation of gas that proves very distressing.

Potassium or sodium bicarbonate is frequently used to lessen excessive acidity of the urine that irritates the bladder, or to alkalinize the urine for the purpose of dissolving mucus. This solvent action is said to explain the occasional breaking down of calculi, into fragments, that had been held together by mucus.

Sodium carbonate is used intravenously, and sodium bicarbonate is often administered by the method known as the "drop enema" in acute acidosis, as well as in acidosis accompanying diabetic coma; but the striking effects seen in the acute form are in marked contrast to the slight or temporary improvement seen in the late stages of diabetes.

Alkalies are commonly used in the treatment of rheumatism and gout, though some authorities maintain that they do harm in gout. Their mode of action is not known. They are also used empirically in the treatment for gallstones and in jaundice.

A solution of sodium bicarbonate is commonly used externally as a solvent for dried exudates in various skin diseases, and as a local application for burns, and other conditions in which the skin is irritated.

(The caustic actions of alkalies are considered elsewhere.)

DOSAGE

Sodium hydroxid and potassium hydroxid are never used internally in the solid state, and their solutions are used less frequently than the bicarbonates. A solution containing only 1 per cent. of sodium hydroxid is disagreeably alkaline to the tongue. One part of a 1 per cent. solution of sodium hydroxid will neutralize about 5 parts of 0.2 per cent. hydrochloric acid; 1 gm. of sodium bicarbonate will neutralize more than 200 c.c. of such dilution of hydrochloric acid, or of gastric juice.

As much as 15 gm. (4 drams) of sodium bicarbonate may be given in a day by the mouth in the treatment of acidosis, and 50 gm. (nearly 2 ounces) may be given in 3 per cent. solution by the drop enema.

When sodium carbonate is given intravenously, care must be exercised in order that none escapes around the vein, as it causes abscess.

When a solution of sodium bicarbonate is boiled in order to sterilize it, it becomes more strongly alkaline to the taste, through the loss of carbon dioxid gas, but its capacity for neutralizing acid is not altered.

In the treatment of rheumatism, the administration of sodium bicarbonate is pushed to the point of rendering the urine alkaline, the actual amount required varying with different individuals.

Doses up to 1.5 gm. (22 grains) have been recommended for bringing up blood and mucus from the stomach in cases in which nausea persists after operation for adenoids.

Potassium bicarbonate is used in doses of 0.2 to 0.3 gm. (3 to 5 grains) dissolved in a small amount of water for the relief of sour stomach with its accumulation of gas.

MATERIA MEDICA

The official alkalies in the order of their popularity are:

Sodii Bicarbonas.—Sodium Bicarbonate, U. S. P., NaHCO_3 , a white, opaque, odorless powder having a cooling, mildly alkaline taste. It is soluble (1:12) in water but insoluble in alcohol. The solution, even

at ordinary temperatures, gradually loses carbon dioxid, and at boiling heat the salt is converted into the normal carbonate.

Potassii Bicarbonas.—Potassium Bicarbonate, U. S. P., KHCO_3 , occurs as colorless, odorless, transparent crystals having a saline and slightly alkaline taste. It is freely soluble (1:3) in water, but practically insoluble in alcohol. Like sodium bicarbonate, this salt in solution gradually loses carbon dioxid, and on boiling is converted into the normal potassium carbonate.

Sodii Carbonas Monohydratus. — Monohydrated Sodium Carbonate, U. S. P., $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$, occurs as a white, granular powder having a strongly alkaline taste. It is freely soluble (1:3) in water, but practically insoluble in alcohol. It should not be confounded with the commercial sodium carbonate, which contains (when uneffloresced) 10 molecules of water of crystallization, and therefore less than half as much Na_2CO_3 as the official salt.

Potassii Carbonas.—Potassium Carbonate, U. S. P., K_2CO_3 , occurs as a white granular powder having an alkaline taste. It is very soluble (1:1) in water, but practically insoluble in alcohol.

Potassii Hydroxidum. — Potassium Hydroxid, U. S. P., KOH , occurs as white sticks or fused masses having a very acrid and caustic taste. It is very soluble (1:0.5) in water and soluble (1:2) in alcohol. Because of its caustic properties it is used internally only in the form of:

Liquor Potassii Hydroxidi.—Solution of Potassium Hydroxid. An aqueous solution of approximately 5 w/v per cent. of KOH .

Sodii Hydroxidum.—Sodium Hydroxid, U. S. P., NaOH . Like potassium hydroxid, this substance occurs in the form of sticks or fused masses. It is very soluble (1:1) in water and in alcohol. Internally it is used only in the form of a solution, preferably a dilution of the official:

Liquor Sodii Hydroxidi.—Solution of Sodium Hydroxid. An aqueous solution of about 5 w/v per cent. of NaOH .

OXYGEN

Leonard Hill and Flack found that the administration of oxygen restored vigor in a striking way, sending the "done" man back into the boxing ring after the third round full of "fire and energy," and reviving the well-nigh exhausted swimmer.

Students were caused to run up and down stairs carrying apparatus that supplied ordinary air or oxygen without their knowing which they breathed, and the performance of the tasks was compared. A greater capacity for doing work was shown by those who breathed oxygen than by those who breathed air, but the differences were not great, and were only such as one might expect, for there is always some embarrassment when one who is untrained performs violent physical effort, because the air way is not sufficient to admit enough air to supply the required oxygen without some extra effort, which was not required when pure oxygen was breathed. In other words, the breathing of oxygen in such cases is equivalent to enlarging the air way and alveolar capacity.

Hill and Flack believe that the inhalation of oxygen prevents the discomfort due to the washing out of carbon dioxide in forced breathing after severe physical effort.

THERAPEUTIC USE

Oxygen is used therapeutically to supply a deficiency in respiration due to mechanical obstruction of the air passages.

The hemoglobin of the blood is incapable of taking up oxygen to the normal degree in poisoning with carbon monoxide (illuminating gas), and if oxygen be supplied under pressure in such cases, as much as 3 per cent. may be dissolved in the plasma, and this supplements that which is taken up by the corpuscles while the oxygen is displacing the carbon monoxide with which the hemoglobin is bound.

Oxygen is used very commonly to relieve respiratory embarrassment in pneumonia, but it is seldom capable of saving life in that disease. Naturally, less labor is required to breathe the requisite amount of oxygen in concentrated than in diluted form through narrowed

air passages, but in severe distress in pneumonia the trouble lies in the diminished surface available for oxygenation of the blood.

MATERIA MEDICA

Oxygenium Compressum.—Compressed Oxygen, N. N. R., gaseous oxygen O_2 in a compressed state, is marketed in several forms of container. The amount of gas present is usually determined by weight, and the degree of pressure of necessity regulates the size and the nature of the cylinder in which the oxygen is sold. Oxygen is a colorless, odorless, tasteless gas, slightly soluble in water and neutral to ordinary indicators. For medicinal purposes, compressed oxygen should be neutral toward litmus and free from chlorin compounds or ozone. The extemporaneous production of oxygen from peroxids, while possible, is not usually considered economically practicable.

THYROID

The removal of the thyroid glands is rapidly fatal in dogs; in man it results in a train of symptoms closely resembling, if not identical with, those seen in myxedema. These include dulness of mentality and a characteristic collection of mucus-like substance in and about the connective tissue of the body.

The symptoms that result from the removal of the thyroid gland can be abolished by the oral administration of the dried gland or of a nonprotein compound containing iodine that may be obtained from the gland and which is probably secreted by it. This iodine compound as separated by Kendall contains 62 per cent. of iodine and is thought to be a di-iodo-di-hydroxy-indole.

The oral administration of iodine or alkaline iodids may give rise to symptoms indicative of increased thyroid activity in those who show a tendency toward hyperthyroidism, or Graves' disease, and this would suggest that the activity of thyroid preparations might be increased by the addition of iodine or iodids to them, but this simple addition of iodine compounds to the thyroid preparations does not

increase their activity. Such sophistication can be detected by chemical analysis, and biologic tests may be used to determine the activity of commercial preparations so that one can be satisfied that there has been no sophistication.

Four general methods have been followed in the investigation of the actions of thyroid preparations. These are: 1. The administration of thyroid substance to thyroidectomized animals. 2. The administration of the gland or preparations of it to patients suffering with myxedema. 3. Metabolism experiments during thyroid feeding. 4. Investigations of the effects of thyroid administration on the circulation.

The results of the oral administration of thyroid substance to thyroidectomized animals and man afford striking proof of the presence of some substance in the gland that is necessary to health, and the results obtained by the therapeutic use of the gland substance or idiothyrene in myxedema, in cretinism and in cases in which the gland has been removed have few parallels in the whole range of therapeutics. These brilliant results have led to the use of the gland substance in innumerable other conditions in which the failure is as complete as the success that attends its proper use.

Moderate doses of thyroid have comparatively little effect on normal persons, but with continued administration there is usually some loss of adipose tissue and some increased protein metabolism with loss of weight.

The action with reference to the increased metabolism of fat and protein is not the same in different individuals. In some there is a marked reduction of fat with relatively little loss of body protein, this being especially common in those persons who accumulate fat readily even when the diet is moderate and exercise is taken habitually.

When thyroid substance is taken for the reduction of fat an abundance of protein should be taken, but there is often a serious disturbance of the nervous

system with marked destruction of body protein even when this precaution is observed.

The injurious effects of excessive thyroid feeding include palpitation with tachycardia and a sense of fulness in the head. There may be lassitude, trembling of the limbs, fever, sweating and sleeplessness. There is usually some looseness of the bowels or severe diarrhea; frequently there is some respiratory depression and there may be exophthalmos. These symptoms are seen in Graves' disease and are almost certainly due to hyperactivity of the gland.

Reid Hunt found that the administration of thyroid substance to mice increased their resistance to poisoning with isonitrile, the degree of the increase in resistance affording an index of the activity of the thyroid used. Unfortunately, we do not know the mechanism by which this tolerance is induced.

The injection of an extract of thyroid substance into the circulation causes slowing of the normal pulse rate, apparently through stimulation of the vagus center in the medulla, but with the appearance of toxic symptoms the vagus loses control of the heart rate and tachycardia results, as previously stated.

The thyroid gland of the sheep is official in the U. S. Pharmacopeia VIII, but sheep are often goiterous, in which case the iodine content and the activity of the gland are low, and much of the older work done with thyroid substance is rendered valueless by the fact that the activity of the substance used is not known.

"New and Nonofficial Remedies" contains a description of a proprietary preparation known as iodothyrene, or thyroiodin, which consists of a milk-sugar trituration of a substance, or mixture of substances, for which it is claimed that 1 gram of the preparation contains 0.3 mg. of iodine. This corresponds fairly well with the official dried thyroid gland.

THERAPEUTIC USES

The uses of thyroid gland have been suggested in part by the discussion that precedes this. First in importance in the use of thyroid stands its employment

in those conditions in which there is a deficiency of normal thyroid activity, including myxedema, sporadic cretinism and patients having enlarged but feebly acting thyroid.

Of less importance, so far as real value is concerned, is its use in obesity though it is probable that it is used for this purpose more frequently than for any other, especially in the form of nostrums advertised directly to the public.

Curiously, its use in myxedema requires greater care than is necessary when it is administered to a normal person. It may then give rise to circulatory disturbances with weak and rapid heart, even when small doses are employed. The cause of these side actions is not known, but it has been suggested that during the course of myxedema and other conditions of deficient thyroid activity certain substances may accumulate in the organism and that these substances may be broken down, or otherwise rendered harmful, by the thyroid, in a manner analogous to the liberation of endotoxins when pathogenic bacteria are destroyed in large numbers in the body during the course of treatment of an infectious disease.

It is probable that the proper regulation of the diet and exercise can always accomplish better results than thyroid in the reduction of superfluous flesh.

The symptoms of thyroid poisoning should be borne in mind when one is called on to treat a patient who may be suspected of having resorted to the use of an obesity cure.

It would not be profitable to attempt to discuss the many different conditions in which thyroid has been used with asserted benefit.

DOSAGE

The average dose of desiccated thyroid gland is said to be 0.1 to 0.6 gm. ($1\frac{1}{2}$ to 10 grains), but it is evident that the dose must be adjusted carefully for each patient.

MATERIA MEDICA

The gland is official as:

Glandulae Thyroideae Siccae—Desiccated Thyroid Gland, U. S. P.

One part of the desiccated gland, in the form of a yellowish amorphous powder, represents approximately 5 parts of the fresh glands of the sheep. To insure greater uniformity it is proposed that the powder be required to yield from 0.17 to 0.23 per cent. of iodine in thyroid combination. The preparation is preferably administered in the form of capsules or cachets.

ANTITHYROID

These may be mentioned here briefly though their use is still in the experimental stage. A somewhat more extended discussion of these preparations will be found in "New and Nonofficial Remedies."

These preparations are obtained from the milk or blood of animals which have been deprived of their thyroid glands.

Their use is based on the theory that the thyroid secretes substances that are toxic but which neutralize, and are neutralized by, other toxic substances formed in the body. Removal of the thyroid is supposed to favor the accumulation of these toxic body substances (not those of the thyroid, of course) in the blood and milk, hence the blood and milk of such animals with the contained hypothetic accumulation are supposed to counteract the effects of hyperthyroidism (Graves' disease) or to interfere with the activity of the gland.

CHAPTER XIV.—SUBSTANCES USED TO INFLUENCE THE APPE- TITE AND DIGESTION

BITTERS

Innumerable bitter drugs have been used with asserted benefit in the treatment of a great number of diseases though there is no satisfactory evidence that they are curative in any of these conditions, and it seems probable that the only benefit derived from their use is to be explained by the improvement in the appetite that they cause. The group of drugs known as simple bitters are now used by educated physicians only for improving the appetite.

That the appetite and digestion are closely related hardly required experimental demonstration, but Pawlow and his co-workers have shown that gastric juice is secreted when a dog is allowed to smell meat, but that food introduced into the stomach through a fistula might remain long undigested.

Bitter substances stimulate the taste buds in the tongue and cause the secretion of saliva, but Carlson and his associates have shown that they do not cause hunger contractions in the stomach, but on the contrary, that when they have any effect they tend to diminish these contractions. These experiments carried out on normal men and on one with a permanent gastric fistula of long standing, leave the question of the influence of the bitters on the appetite, as distinguished from hunger sensations, undecided.

Abundant clinical experience seems to show that the bitters taken shortly before meals improve the appetite in suitable cases. From this it follows that the subject is one for clinical, rather than purely pharmacologic discussion.

Bitters are classified conveniently as simple and aromatic. There are innumerable simple bitters, but the list of drugs in this class now recognized by the Pharmacopeia is much smaller than formerly and "Useful Drugs" contains only one—gentian—that may be classified as a simple bitter, since others, including nux vomica and cinchona, that may be used as such, have more important actions.

Chamomile, bitter orange peel and serpentaria are frequently added to alcoholic beverages or "bitters" in domestic practice, but none of these aromatic bitters has been included in "Useful Drugs."

Gentian is administered a few minutes before meals in such a way that the bitter taste is utilized, for, as previously stated, it has no therapeutic effect aside from this bitter taste.

DOSAGE

Gentian is rarely used in substance; the dose of the solid extract is 0.25 gm. (4 grains); that of the compound tincture is 4 c.c. (one teaspoonful).

MATERIA MEDICA

Extractum Gentianae.—Extract of Gentian, U. S. P., is an aqueous extract of gentian evaporated to pilular consistence. As suggested above, this preparation is of no direct value as a bitter unless dissolved in water and its continued use as a diluent in the making of pills is probably due to a misapprehension.

Tinctura Gentianae Composita.—Compound Tincture of Gentian, U. S. P., is a hydro-alcoholic tincture representing 10 per cent. of gentian with bitter orange peel and cardamom used for flavoring. It should be directed to be well diluted, but not followed with water, so as to allow the bitter taste to become evident.

AROMATIC CARMINATIVES

Under this classification are included various drugs that are related to other groups. Bastedo enumerates no less than eighteen therapeutic groups in which the carminatives may be classified. These include:

1. Anticolics, especially for infants (anise, ginger and peppermint).
2. Odors and flavors.
3. Correctives of irritant cathartics.
4. For tympanites—in typhoid fever, pneumonia, etc.
5. Anthelmintics (oil of chenopodium).
6. Stimulants of mucous membranes.
7. Antiseptics and anesthetics.
8. Counterirritants.
9. Stimulants in chronic skin diseases.
10. Stimulants to the growth of hair (oil of mace).
11. Antirheumatics (methyl salicylate).
12. Antihysterics (asafetida, camphor).
13. Antiasthmatics (cubeb in powder for cigarettes).
14. Bronchial stimulants.
15. Diuretics.
16. Urinary antiseptics.
17. Emmenagogues.
18. Leprosy (oil of chaulmoogra).

Some of these have been discussed and a few remain to be considered.

The aromatic carminatives increase gastro-intestinal peristalsis and serve to hasten the passage of gas through the stomach and bowel. They induce hyperemia of the gastro-intestinal mucous membranes and probably increase the appetite and digestion.

Capsicum enjoys a special reputation in the treatment of atonic dyspepsia due to chronic alcoholism; cardamom is used as an aromatic carminative and the compound tincture is also used to give a handsome appearance to alcoholic mixtures. Oil of cloves is very commonly used for the relief of pain in carious teeth. Cinnamon is especially popular as a flavor. Mustard is most commonly used as a condiment; its use as a counterirritant has been mentioned. Ginger is probably the most popular member of the group for the relief of colic.

DOSAGE

The average dose of tincture of capsicum is 0.5 c.c. (8 minims); that of tincture of cardamom is 5 c.c. (75 minims); of tincture of ginger 2 c.c. (30 minims). Oil of cloves is seldom used internally and oil of cinnamon is used mainly for flavoring. The dose of oil of cloves is 0.2 c.c. (3 minims); that of oil of cinnamon is 0.1 c.c. (2 minims).

MATERIA MEDICA

Among the more widely used preparations that are generally classed as carminatives, we have:

Tinctura Capsici.—Tincture of Capsicum, U. S. P., a 10 w/v per cent. preparation with 90 per cent. alcohol.

Tinctura Cardamomi.—Tincture of Cardamom, U. S. P., a 20 w/v per cent. solution in diluted alcohol. The compound tincture of cardamom, *Tinctura Cardamomi Composita*, is a 2.5 w/v per cent. diluted alcohol preparation of cardamom with cinnamon and caraway, colored red with cochineal.

Tinctura Zingiberis.—Tincture of Ginger, U. S. P., a preparation containing 2 w/v per cent. of the drug in alcohol.

Oleum Caryophylli.—Oil of Cloves, U. S. P., a volatile oil containing about 80 per cent. of eugenol.

Oleum Cinnamomi.—Oil of Cinnamon, U. S. P., a volatile oil required to contain about 75 per cent. of cinnamic aldehyd.

PEPSIN, PANCREATIN AND HYDROCHLORIC ACID

There are few chapters on therapeutics that reflect less credit on us than that dealing with the abuse of the digestive ferments. Many physicians have clung tenaciously to the idea that intestinal digestion can be promoted by the administration of pancreatin or mixtures of pepsin and pancreatin, despite the frequent reiteration of the fact that pepsin destroys pancreatin in the presence of a suitable acid.

Pepsin may be given to secure the digestion of protein food in the stomach when there is a deficiency of

pepsin in the gastric secretion, but this seldom occurs, pepsin being secreted even where there is a deficiency of hydrochloric acid in the stomach.

Pepsin acts only in acid mediums and its action is inhibited when the concentration of hydrochloric acid exceeds 0.3 per cent. It is destroyed rapidly by pancreatin in alkaline mediums.

Pepsin is used in acute indigestion when there is no absence of hydrochloric acid in the gastric secretion but in chronic conditions it should be used only when it has been shown that pepsin and hydrochloric acid are both deficient in the gastric secretion.

Pancreatin is not often suited for oral administration for the reasons just mentioned, and it is useful mainly for preparing partially digested protein and starchy foods.

It may be administered with sodium bicarbonate in achylia gastrica, and it has been administered in the form of pills coated with salol or in gelatin capsules that have been hardened in formaldehyd, but this method of administration is not very promising.

Milk may be partially peptonized by adding a small amount of pancreatin and bicarbonate of sodium and allowing it to stand for a few minutes at body temperature. The process may be stopped by heating the milk rapidly to 65 C. (150 F.). If the process is carried too far the taste becomes excessively bitter.

As previously stated, there is a deficiency of hydrochloric acid in the gastric secretion more frequently than of pepsin. It is commonly given in doses of 1 c.c. (15 minims) of the diluted acid with water.

MATERIA MEDICA

The above drugs are official as:

Pepsinum.—Pepsin, U. S. P., the ferment or enzyme obtained from the stomach of the hog, capable of digesting not less than 3,000 times its own weight of freshly coagulated and disintegrated egg albumin.

Pancreatinum.—Pancreatin, U. S. P., a mixture of enzymes contained in the pancreas of warm-blooded animals capable of converting not less than 25 times its own weight of starch into substances soluble in water.

Acidum Hydrochloricum Dilutum.—Diluted Hydrochloric Acid, U. S. P., should contain 10 per cent. by weight of absolute hydrochloric acid.

COD LIVER OIL

Cod-liver oil may be considered in this place, though it is not a drug, its value depending on its nutrient property.

The taste is so disagreeable to most persons that it is commonly dispensed in the form of a sweetened and flavored emulsion.

Cod-liver oil has long enjoyed a special reputation in the treatment of tuberculosis. Practically all proprietary emulsions of cod-liver oil contain the useless and extremely disagreeable hypophosphites.

The following formulas may be used by those who prefer to prescribe the emulsion of cod-liver oil without useless salts:

	gm. or c.c.	
Cod liver oil.....	250	℥ viii
Acacia	60	℥ ii
Syrup	60	℥ ii
Methyl salicylate	2	℥ xxx
Water, a sufficient quantity make	500	℥ xvi

The flavoring may be varied to suit the individual taste; oil of sassafras, oil of peppermint, oil of cinnamon or oil of bitter almond may be used in varying quantities. In the event that oil of bitter almond is used that without hydrocyanic acid should be specified.

An emulsion made with yolk of egg has had considerable vogue at times and may be made as follows:

	gm. or c.c.	
Cod liver oil.....	250	℥ viii
Fresh yolk of eggs.....	45	℥ jss
Glycerin	60	℥ ii
Syrup	60	℥ ii
Methyl salicylate	2	℥ xxx
Water, a sufficient quantity to make.....	500	℥ xvi

In making this emulsion the yolk of eggs is triturated in a mortar with the glycerin added gradually. The oil is then added to this mixture, small portions at a time, followed by the syrup, the flavoring and finally

a sufficient amount of water to make the required quantity.

MATERIA MEDICA

The oil is officially described as:

Oleum Morrhuae.—Cod-Liver Oil, U. S. P., a fixed oil obtained from the fresh liver of various species of cod.

FLAVORS, DILUENTS AND VEHICLES

SACCHARIN

Saccharin (benzosulphinid) is used by diabetics as a substitute for sugar, though it is not at all satisfactory. It is frequently stated that saccharin is nontoxic, and very large amounts have been administered to a dog during a period of ten days without inducing perceptible ill effects. It has also been used to replace sugar to a large extent in sweetened beverages, but unfortunately we do not know whether its continued use is capable of inducing deleterious effects under abnormal conditions, and in the present state of our knowledge it should not be used in place of sugar unless the latter is contraindicated. It is unfortunate that our knowledge of the subject is so limited, because many persons who crave sweets are singularly intolerant of sugar and are subject to attacks of indigestion with headache and other evidences of severe intoxication after even moderate indulgence in sugar.

Commercial saccharin is variable in composition, and is usually sold on the basis of its sweetening power compared to sugar. The product is official as:

Benzosulphinidum.—Benzosulphinid, saccharin, U. S. P., the anhydrid of ortho-sulphanid-benzoic acid or benzosulphonic-imid, having approximately 500 times the sweetening capacity of sugar. It occurs as a white crystalline nearly odorless powder having an intensely sweet taste. It is soluble (1:25) in alcohol but only slightly soluble (1:250) in water. The addition of an alkali materially increases the solubility, and the product usually sold as "soluble saccharin" is made by neutralizing a solution of saccharin with sodium carbonate or bicarbonate and evaporating to dryness.

This soluble form of saccharin is generally sold in the form of compressed tablets or of tablet triturations containing the equivalent of 15, 30 or 60 mg. ($\frac{1}{4}$, $\frac{1}{2}$ or 1 grain) of pure saccharin. The tablet containing 30 mg. is equivalent to 15,000 mg., 15 grams or approximately 1 tablespoonful of sugar. The proportion usually employed is 0.03 gm. ($\frac{1}{2}$ grain) of saccharin or 0.6 gm. (1 grain) of soluble saccharin to 200 to 250 gm. (6 to 8 ounces) of fluid. In practice it will usually be found necessary to use rather more than the actual sweetening capacity of saccharin unless some addition in the form of milk, albumin, gum, gelatin or casein can be made to the liquid to increase its density. In lieu of the tablets of soluble saccharin, an alcoholic or hydroalcoholic solution of saccharin itself may be directed to be used, or an extemporaneously prepared solution of saccharin may be prescribed as follows:

	gm. or c.c.	
Saccharin	3	gr. xlv
Sodium bicarbonate	15	gr. xxii
Water, a sufficient quantity to make....	200	fl. § vi

Dissolve the saccharin and sodium bicarbonate, by means of gentle heat if necessary. One teaspoonful of the resulting solution is equivalent to about 0.06 gm. (1 grain) of saccharin.

The following substances that have been included in the list of "Useful Drugs" do not require detailed discussion:

Mentha Piperita.—Peppermint, U. S. P. The leaves and tops of *Mentha piperita*. Peppermint is practically never used therapeutically in substance, but is sometimes employed pharmaceutically to give a green color to alcoholic preparations, such as spirit of peppermint.

Aqua Menthae Piperitae. — Peppermint Water, U. S. P. A saturated solution of peppermint oil in water. It is used largely as a vehicle, especially for the bromids.

Oleum Menthae Piperitae. — Oil of Peppermint, U. S. P. This is actively carminative. The dose is 0.2 c.c. (3 minims) administered on sugar preferably.

Spiritus Menthae Piperitae.—Spirit of Peppermint, U. S. P. It contains 10 per cent. of the oil in alcohol

colored with the herb. It is sometimes used as flavoring, but it is also actively carminative. The dose is 2 c.c. (30 minims), diluted with water or syrup and water.

The flavor of spearmint is preferred by many to that of peppermint. Spearmint herb, oil, spirit and water are also official. These correspond to the preparations of peppermint in activity.

Rosa.—Rose, U. S. P. It is seldom used therapeutically in substance.

Aqua Rosae.—Rose Water, U. S. P. A solution of the volatile oil of rose in water. It is much used as a perfume in lotions and toilet articles.

Oleum Rosae.—Oil of Rose, U. S. P. It is used to perfume ointments, 1 or 2 drops being sufficient for an ounce of ointment.

Saccharum Lactis.—Sugar of Milk, U. S. P. It is used as a diluent, especially for powders and tablet triturates. It is also used extensively for modifying milk in infant feeding, and of late it has come into use in the high calory diet in typhoid fever as advocated especially by Shaffer and Coleman.

Syrupus Sarsaparillae Compositus. — Compound Syrup of Sarsaparilla, U. S. P. A mixture of fluidextract of sarsaparilla (20 c.c.), fluidextract of glycyrrhiza (1.5 c.c.), fluidextract of senna (1.5 c.c.) and aromatics, with syrup (sufficient to make 100 c.c.).

Compound syrup of sarsaparilla was formerly used as a so-called blood purifier, or alterative, but at present it is used as a vehicle, especially for potassium iodid. A simple syrup of sarsaparilla affords a thick froth with "soda water," and this is commonly used for the administration of castor oil. The compound syrup may be used for the purpose, but it is too bitter to be pleasant to children.

Sugar and syrup are widely used in pharmacy, but they do not require further mention here. Sarsaparilla (the root) is of no therapeutic interest except that it contains saponin.

CHAPTER XV.—ANTHELMINTICS

Anthelmintics are agents that kill intestinal parasites or facilitate their expulsion with the aid of evacuants.

The ideal anthelmintic would kill or stupefy the parasites but would not be absorbed from the gastrointestinal tract of the host, nor would it irritate the stomach or the bowel more than enough to cause purgation. Unfortunately, the best of the anthelmintics at our disposal are far from being ideal, and all of them are capable of causing the death of the patient if used without care, while none of them is certain in its action on the parasites.

The round worm (*Ascaris lumbricoides*) and pinworm (*Oxyuris vermicularis*) are probably the most common of this type of parasite in the bowels of children, if we except the hookworm, which is very prevalent in certain parts of the country, while the tapeworm, including the *Taenia* and *Bothriocephalus latus* (or broad tapeworm) are found more commonly in adults than in children, but taeniae are occasionally reported as occurring in children and a case of *Taenia saginata* has been very recently reported as occurring in an infant.

Gross parasites of this nature can be guarded against more easily than the bacterial infections, and the more common sources of infection should be understood more generally than is the case.

The so-called head, which is of minute size, is the real tapeworm, all the remainder, the segments, consisting of generative buds containing matured sexual organs. These are constantly breaking off and passing out of the bowel, the ova being swallowed by other animals in which they develop in various organs. For example, the hog is commonly infested with *Taenia solium*, which becomes encysted, forming what is known as "measles," and when a person eats raw measly pork he becomes the host of a tapeworm,

Taenia solium. It is probably the tapeworm most commonly found in this country. *Taenia saginata* may infest beef in the same way. *Bothriocephalus latus* is very much more common in Europe, but it is occasionally seen in this country.

The dog is commonly infested with intestinal parasites, which are sometimes present in large numbers. Other domestic and wild animals are similarly infested.

While the eating of raw meats, especially pork, is probably the commonest source of infestation, the possibility of having the hands contaminated by pets should be borne in mind.

All active cathartics tend to remove worms and other intestinal parasites in the evacuations, but while this may occasionally succeed in ridding one of the so-called head of the tapeworm, as a rule only a smaller or larger number of segments are thus gotten rid of and these segments are rapidly replaced.

As previously stated, none of the anthelmintics is either certain in its action or free from danger; hence every precaution should be taken to insure the most favorable conditions for the expulsion of the parasite when medication is undertaken.

Medication should be preceded by a diet calculated to weaken the parasite as much as possible without greatly weakening the patient. Meat and other proteins are withheld or given in small amounts while carbohydrates are given in abundance. It is said that sharp particles, such as seeds of strawberries, and pungent substances, such as mustard, tend to cause the parasite to loosen its hold; hence these may be utilized as a preliminary to active treatment.

Tapeworms are provided with suckers, hooks or serrated margins by which they attach themselves to the mucous membrane of the intestine, and the best that can be accomplished by anthelmintics, as a rule, is to stupefy the parasite or paralyze its musculature so that its hold on the intestinal mucous membrane is released, at which time it may be swept out in a copious watery evacuation.

The patient should fast for about twelve hours before taking a taeniafuge, such as aspidium or pelle-

tierin, but a cup of coffee may be taken in the morning on arising, that is, shortly before the administration of the drug.

A laxative may be administered previously so as to insure the almost complete emptying of the intestine, but an entirely empty tract facilitates the absorption of the drug by the host.

The parasite is usually caused to loosen its hold within an hour or two after the administration of an effective dose of aspidium; hence the purgative is usually given either at the same time or shortly after the anthelmintic.

The pinworm, or threadworm (*Oxyuris vermicularis*), is a very small parasite that inhabits the lower parts of the intestine in great numbers. It does not attach itself to the intestinal mucous membrane and may be dislodged from the bowel by cathartics and enemas.

Bastedo mentions the following as being used for irrigating the colon to remove the pinworm: infusion of quassia; lime water; quinin bisulphate 1:2,000; a solution of tannin or alum 2 gm. (30 grains) to 500 c.c. (1 pint) of water; or 15 c.c. ($\frac{1}{2}$ ounce) of oil of turpentine to 1 liter (1 quart) of soap suds.

He states that the *Taenia nana* is often mistaken for pinworm and one of the dwarf tapeworms is said to be the commonest of the tapeworms of childhood.

ASPIDIUM

Our knowledge of the chemistry of aspidium is unsatisfactory, but there are several substances, including amorphous and crystalline filicic acid, on which the anthelmintic actions of the drug seem to depend. Whatever the nature of the active principles, they are present in the oleoresin, in which form aspidium is now commonly employed.

Under favorable conditions but little of the oleoresin (or its active constituents) is absorbed into the circulation in man, but when absorption does occur severe, and even fatal, poisoning may result.

Nausea and even slight vomiting are not infrequent consequences of therapeutic doses, and this may even

prevent the desired action of the drug. With absorption and severe poisoning there are violent vomiting and purging with pain in the intestines, muscular weakness and convulsions, followed by stupor passing into coma. Castor oil is sometimes administered with aspidium or afterward in order to induce purgation, but there seems to be little doubt that, because of the readiness with which it dissolves the active principles of aspidium, it promotes absorption unless purgation is prompt.

It is stated that aspidium is less effective against taeniae than against *Bothriocephalus*. It is unfortunate that this point has not been determined with certainty, for aspidium is widely used for tapeworm regardless of the species infesting the patient.

PELLETIERIN TANNATE

The bark of pomegranate root has long been used in the treatment of tapeworm, but it contains an abundance of tannin and this often gives rise to vomiting when an infusion is employed in the dose necessary to act as a taeniafuge — from 30 to 60 gm. (1 to 2 ounces) — hence the tannate or sulphate of the alkaloid, pelletierin, is now almost always used instead of the bark.

Pelletierin is sometimes absorbed from the gastrointestinal tract, causing stimulation of the central nervous system, and a veratrin-like action on the muscles. It seems probable that a similar action on the musculature of the tapeworm explains its efficiency as a taeniafuge. Poisonous doses of pelletierin cause dizziness and sometimes disturbance of vision in addition to the muscular weakness.

SANTONIN

Santonin is probably the most effective anthelmintic available for the expulsion of the round worms of childhood. According to von Schroeder santonin does not kill the worm but renders the intestinal contents unpleasant, causing the parasite to seek the large bowel, from which it is expelled by the cathartic that is used in the treatment.

Sodium santoninate is soluble and this is probably absorbed into the circulation of the patient more rapidly than the insoluble santonin; hence the coarsely powdered crystals of santonin are generally directed to be used.

Santonin is always absorbed to some extent and gives the urine a deeper yellow or red color if it be alkaline. Poisoning rarely follows the administration of suitable doses of santonin, but frequently objects appear violet colored and later yellow, after its administration, and convulsions may result from poisonous doses.

OIL OF CHENOPODIUM

Oil of chenopodium or oil of American wormseed has long been used in the treatment of round worms of children, and of late it has attracted attention in the treatment of hookworm. Two investigators reported that they used it in the treatment of nearly 1,500 cases of hookworm with more frequent success than was attained with thymol or other means.

They administered three doses, each containing 16 drops of oil of chenopodium, at intervals of two hours, and after another interval of two hours they administered a tablespoonful of castor oil to which they added a large dose of chloroform.

The oil of chenopodium does not kill the parasite but narcotizes it and it must be expelled by means of a cathartic, castor oil being employed frequently.

Several cases of severe or fatal poisoning by oil of chenopodium have been recorded and the drug should be used with caution.

THYMOL

Thymol has come to be used widely in the treatment of hookworm disease, but the danger of poisoning with the large doses required leaves much to be desired.

At the present time the supply of thymol is said to be extremely limited, and there would appear to be no reason why the generally safer oil of chenopodium should not be used in its place.

DOSAGE

The average dose of oleoresin of aspidium is given as 2 c.c. (30 minims), but larger amounts are frequently used.

The average dose of pelletierin tannate is 0.25 gm. (4 grains) and it is stated in "Useful Drugs" that not more than 0.3 gm. (5 grains) should be given at once, as that amount has caused paralysis, but Meyer and Gottlieb state that doses of 0.3 to 0.4 gm. (5 to 6 grains) of the sulphate or the tannate usually act efficiently without causing severe symptoms of poisoning. These authors advise the administration of 0.5 to 1 gm. (8 to 15 grains) of tannin with the tannate or sulphate to insure that the alkaloid be maintained in the intestine in the form of the insoluble tannate.

It may be given preferably in the form of capsules after the usual preliminary attention to the diet and emptying of the intestinal tract, and it is best followed in two hours by a brisk cathartic, such as castor oil or magnesium sulphate.

The average dose of santonin is 0.065 gm. (1 grain). Since santonin does not kill or even severely injure the worm it is better practice to give the drug for several days. Lozenges, containing 0.03 gm. ($\frac{1}{2}$ grain) santonin may be given to a child morning and evening for three days; twice as much is used for an adult. The last dose is to be followed by a purgative such as calomel, or a laxative dose of calomel, 0.005 gm. ($\frac{1}{12}$ grain), may be administered with each dose of santonin.

The dose of oil of chenopodium is given as 0.2 c.c. (3 minims) in the pharmacopeia, but this appears to be rather too conservative. But it would be wise to avoid the use of large doses of chloroform after maximal doses of the oil, for chloroform, which is itself an active anthelmintic in large doses, is usually considered too poisonous for common use for this purpose.

The dose of thymol in the treatment of hookworm disease is as follows: For children under 5 years, the fine powder is given in doses of 0.5 gm. (8 grains); from 5 to 10 years, 1 gm. (15 grains); from 10 to 15

years, 1.5 gm. (22 grains) ; from 15 to 20 years, 2 gm. (30 grains) ; and over 20 years, 3 to 4 gm. (45 to 60 grains).

It is especially necessary to prevent its absorption when such large doses are used ; hence oils and fats should be avoided in the diet.

MATERIA MEDICA

Of the preparations used as anthelmintics, the more popular are :

Oleoresina Aspidii. — Oleoresin of *Aspidium*, U. S. P., a semisolid dark green extract. On standing it usually deposits a granular crystalline substance which should be thoroughly mixed with the liquid portion before use.

Pelletierinae Tannas. — Pelletierin Tannate, U. S. P., a mixture of alkaloids, obtained from pomegranate, which occurs as a light, odorless amorphous powder that is only slightly soluble (1 : 235) in water, but soluble (1 : 12.5) in alcohol.

Santoninum. — Santonin, U. S. P., the inner anhydrid or lactone of santonic acid, a glucosid obtained from *santonica*. It occurs in colorless crystals that become yellow on exposure to light and air. Santonin is very insoluble (1 : 5,300) in water, but soluble (1 : 35) in alcohol.

Oleum Chenopodii. — Oil of *Chenopodium*, U. S. P., a limpid, yellowish liquid having a peculiar somewhat camphoraceous odor and a pungent, slightly bitter taste.

Thymol. — For materia medica of thymol see under Antiseptics and Disinfectants.

CHAPTER XVI.—SERUMS, VACCINES AND VIRUSES

Serums, vaccines and viruses constitute one of the most important groups of remedial agents in the materia medica, but the comprehensive discussion of their uses belongs to a special department of medicine, and only the briefest consideration of them is required here. (A brief but somewhat more extended discussion of this class of agents will be found in New and Nonofficial Remedies for 1915, p. 279.)

The commercial manufacture of these agents is under the supervision of the United States Public Health Service. Standards of potency are provided for antidiphtheric and antitetanic serums, but there is no standard of therapeutic efficiency for the other serums, or the vaccines or viruses. They are examined to see that they are not contaminated with bacterial or other harmful substances, but this does not insure the usefulness of any of them, since many of them are in themselves capable of doing harm.

MATERIA MEDICA AND DOSAGE

In the order of their introduction into the medicine, the several more widely used products may be arranged as follows:

Virus Vaccinum.—Vaccine Virus, N. N. R., is defined as the material obtained under aseptic conditions from skin eruptions of calves having vaccinia. It is usually marketed in capillary tubes or as glycerinated points, and is used for immunization against smallpox, the contents of one tube or point constituting the dose, which is usually applied endermatically with the usual surgical precautions.

Antirabic Vaccine or Antirabic Virus, N. N. R., is the virus of rabies rendered practically nonvirulent for man by passage through a series of rabbits. The material used consists of sections of the spinal cords

of the infected rabbits dried for different periods of time and preserved in glycerin. For use, this material is emulsified in physiologic saline solution and injected into the subcutaneous tissue of the anterior abdominal wall to develop an immunity to rabies before the normal incubation period of the disease is concluded. As the individual dose should be prepared shortly before injection, the material is usually obtained direct from the producer. A list of the laboratories licensed to make antirabic vaccine will be found in N. N. R.*

Tuberculinum.—Tuberculin, N. N. R. This product essentially represents the toxins of the tubercle bacillus, and is marketed in a variety of forms, either as a filtered extract of the bacilli or as the pulverized insoluble substance of the dead bacilli themselves. The tuberculins are used in the diagnosis, treatment and prophylaxis of tuberculosis; a number of the more widely used or more prominent forms are enumerated in N. N. R. Tuberculin is of value principally as a diagnostic agent. The characteristic properties of the trade product to be used should be studied closely before it is employed.

Serum Antidiphthericum.—Antidiphtheric Serum, Diphtheria Antitoxin, U. S. P., a fluid separated from the coagulated blood of the horse immunized through the inoculation of diphtheria toxin. Antidiphtheric serum is now being marketed in the form of the normal serum, the purified serum or antidiphtheric globulins, and the dried serum. It is required that the potency of these products shall be stated in terms of the standard unit established by the United States Public Health Service.

Diphtheria antitoxin has the power of combining with, and of neutralizing the toxin formed by, the diphtheria bacillus. The important object in the administration of the antitoxin is to give it early enough and in sufficient dosage to nullify the toxin as it is produced. For the average case of diphtheria, it is customary to administer 10,000 units of antitoxin subcutaneously, as soon after the discovery of the

* Facts and Problems of Rabies (Hyg. Lab. Bull. 65, U. S. P. H. S.) will be found interesting.

disease as possible. For cases more than twenty-four hours after onset, or cases already well developed or which seem to be of a virulent, rapidly spreading type, this dose must be materially increased.

Serum Antitetanicum. — Antitetanic Serum, or Tetanus Antitoxin, U. S. P., a fluid separated from the coagulated blood of the horse actively immunized against tetanus toxin. Its physical properties are similar to those of diphtheria antitoxin, and like the latter, it is being marketed in the form of normal serum, purified serum or antitetanic globulins and dried serum, all of which are labeled to show the number of standard antitoxin units as defined by the United States Public Health Service.

Tetanus antitoxin is used chiefly as a prophylactic in connection with deep or lacerated wounds, especially those exposed to dust or dirt. The antitoxin may be administered subcutaneously or may be introduced directly into the wound, in the form of the dried serum, as a part of the dressing, or both. As a curative agent, in the developed disease, it is generally agreed that the antitoxin should reach the nerve centers as quickly as possible and in as high a concentration as possible; therefore, intraspinal injection is usually employed.

As a prophylactic agent, antitetanic serum is administered in doses of 1,500 units, injected subcutaneously, and repeated in twenty-four hours if thought necessary. As a curative agent, it is administered in doses of 5,000 units intraspinally, or 10,000 units intravenously, to be repeated subcutaneously as indicated.

Vaccinum Typhosum.—Typhoid Vaccine, N. N. R., prepared from *Bacillus typhosus*, with or without the addition of *Bacillus paratyphosus* A and *Bacillus paratyphosus* B. Typhoid vaccine is of recognized utility in the prevention of typhoid fever. The immunity produced may persist from two to four years or longer. It is also of service in the treatment of typhoid carriers, though its use in the treatment of typhoid fever itself has given very inconclusive results.

As a preventive, typhoid vaccine should be administered only to healthy persons. The initial dose usually

represents 500 million bacilli, and is followed in from seven to ten days by a second injection representing approximately 1,000 million bacteria. Some authorities recommend that a third injection of the same size be given in from seven to ten days after the second.

Vaccinum Staphylococcicum.—*Staphylococcus Vaccine*, N. N. R., may be prepared from *Staphylococcus aureus*, *Staphylococcus pyogenes albus*, or *Staphylococcus pyogenes citreus*, or from all three. *Staphylococcus vaccine* is used in carbunculosi, furunculosis, sycosis and certain cases of acne, as a curative agent. An autogenous vaccine is usually considered to be preferable, but if this cannot be prepared, it is desirable to at least determine the nature of the infection by bacteriologic examination.

For the initial dose, it is customary to administer the equivalent of from 200 to 500 million organisms, followed by double this dose in from seven to ten days.

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represents 500 million bacilli, and is followed in from seven to ten days by a second injection representing approximately 1,000 million bacteria. Some authorities recommend that a third injection of the same size be given in from seven to ten days after the second.

Vaccinum Staphylococcicum.—*Staphylococcus* Vaccine, N. N. R., may be prepared from *Staphylococcus aureus*, *Staphylococcus pyogenes* albus, or *Staphylococcus pyogenes citreus*, or from all three. *Staphylococcus* vaccine is used in carbunculosi, furunculosis, sycosis and certain cases of acne, as a curative agent. An autogenous vaccine is usually considered to be preferable, but if this cannot be prepared, it is desirable to at least determine the nature of the infection by bacteriologic examination.

For the initial dose, it is customary to administer the equivalent of from 200 to 500 million organisms, followed by double this dose in from seven to ten days.

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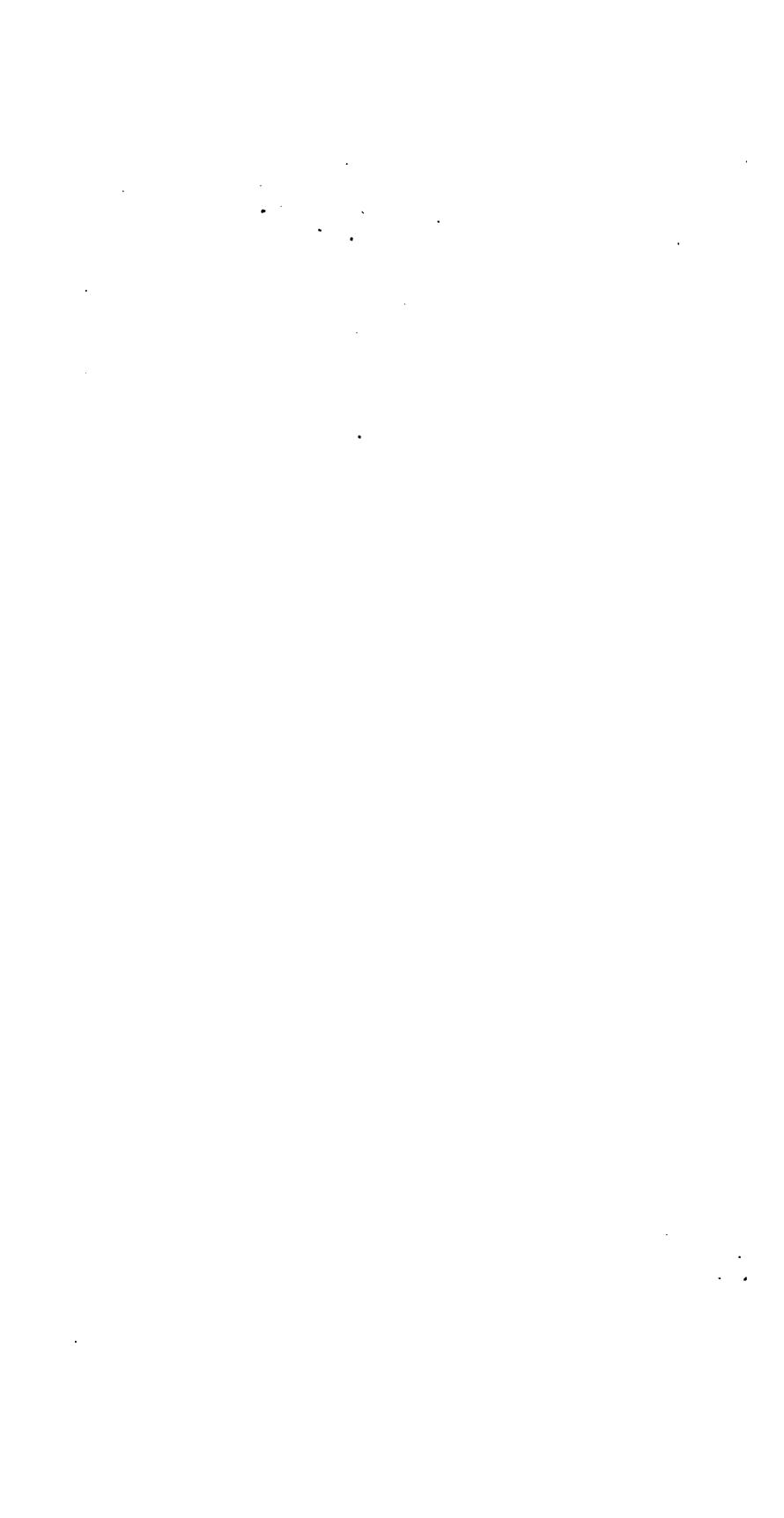
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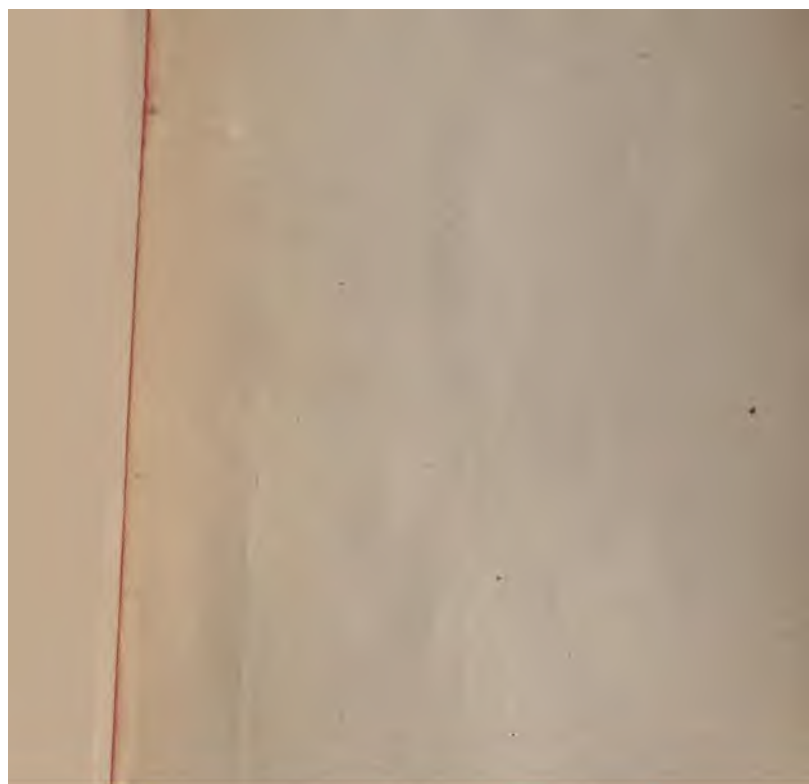
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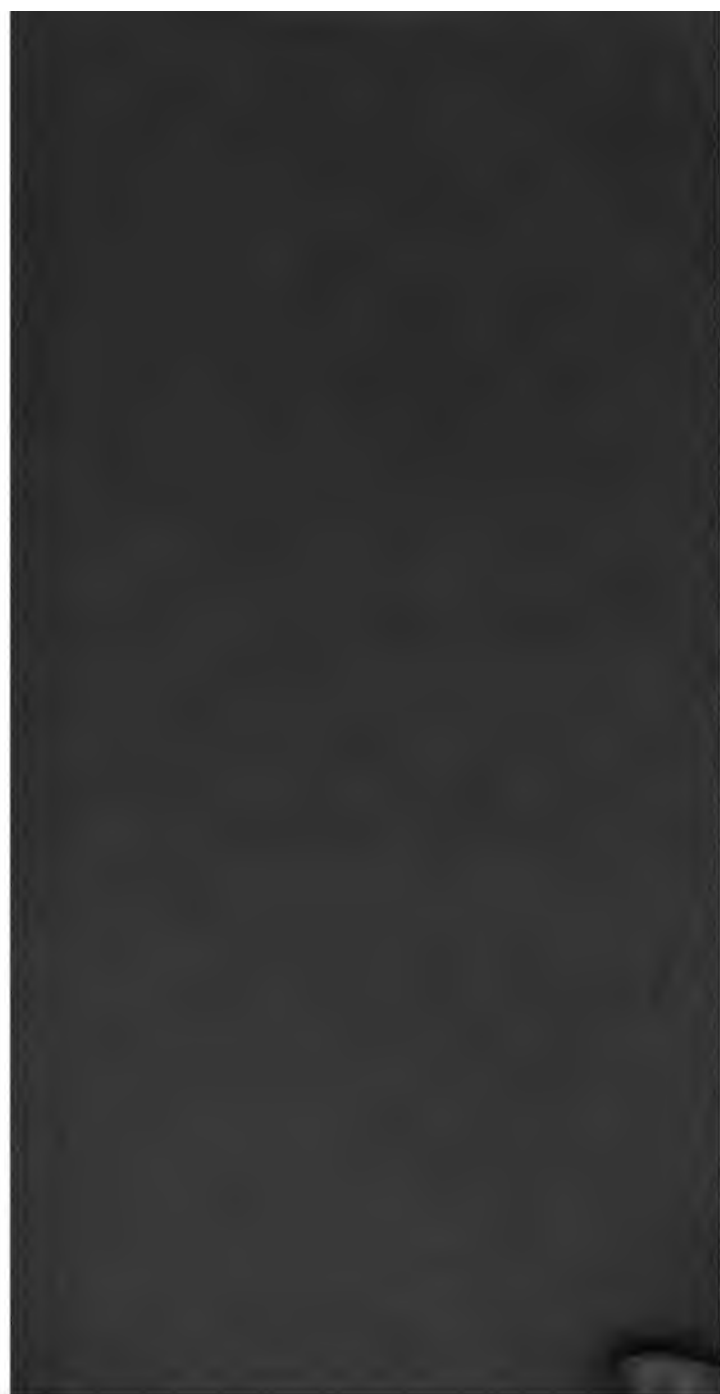
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